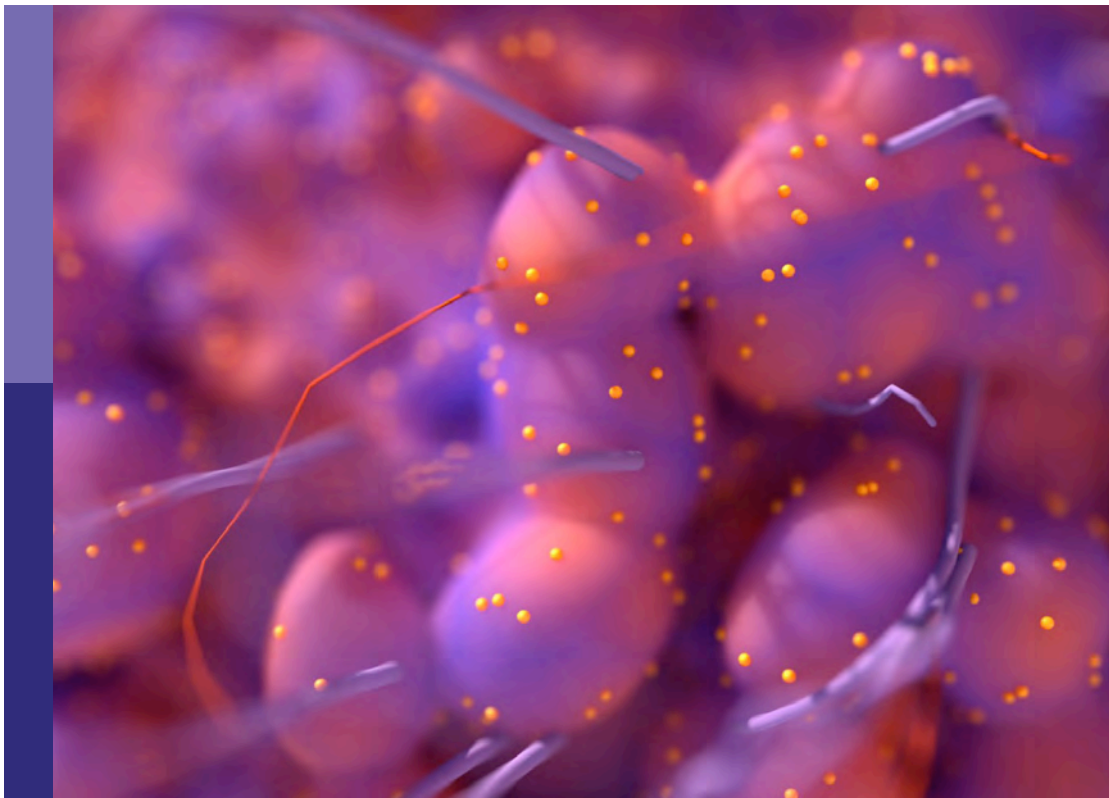
frontiers | Research Topics

# Exercise, physical therapy and wellbeing in breast cancer patients

**Edited by**
Julio de la Torre and Jose Angel Garcia-Saenz

**Published in**
Frontiers in Oncology



ISSN 1664-8714
ISBN 978-2-83251-787-1
DOI 10.3389/978-2-83251-787-1

## About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

## Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

## Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

## What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

# Exercise, physical therapy and wellbeing in breast cancer patients

**Topic editors**

Julio de la Torre — Comillas Pontifical University, Spain

Jose Angel Garcia-Saenz — Health Research Institute of the Hospital Clínico San Carlos (IdISSC), Spain

**Citation**

de la Torre, J., Garcia-Saenz, J. A., eds. (2023). *Exercise, physical therapy and wellbeing in breast cancer patients*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-83251-787-1

# Table of contents

05 Editorial: Exercise, physical therapy, and wellbeing in breast cancer patients
Julio C. de la Torre-Montero, Soraya Casla-Barrio, Blanca Herrero-López and José Ángel García-Saénz

08 Association of Insomnia, Depressive Disorders, and Mood Disorders as Risk Factors With Breast Cancer: A Nationwide Population-Based Cohort Study of 232,108 Women in Taiwan
Hui-Pu Liu, James Cheng-Chung Wei, Hei-Tung Yip and Ming-Hsin Yeh

21 Longitudinal Assessment of Physical Activity, Fitness, Body Composition, Immunological Biomarkers, and Psychological Parameters During the First Year After Diagnosis in Women With Non-Metastatic Breast Cancer: The BEGYN Study Protocol
Cosima Zemlin, Caroline Stuhlert, Julia Theresa Schleicher, Carolin Wörmann, Laura Altmayer, Marina Lang, Laura-Sophie Scherer, Ida Clara Thul, Carolin Müller, Elisabeth Kaiser, Regine Stutz, Sybelle Goedicke-Fritz, Laura Ketter, Michael Zemlin, Gudrun Wagenpfeil, Georges Steffgen and Erich-Franz Solomayer

35 Physical Therapies for Psychosomatic Symptoms and Quality of Life Induced by Aromatase Inhibitors in Breast Cancer Patients: A Systematic Review and Meta-Analysis
Xue-Ying Zhu, Zhong Li, Cong Chen, Ru-Li Feng, Bai-Ru Cheng, Ruo-Yi Liu, Rui-Ting Wang, Li Xu, Yue Wang, Xin Tao and Peng Zhao

51 Adapted Physical Activity for Breast Cancer Patients Treated with Neoadjuvant Chemotherapy and Trastuzumab Against HER2 (APACAN2): A Protocol for a Feasibility Study
Angeline Ginzac, Maureen Bernadach, Ioana Molnar, Martine Duclos, Emilie Thivat and Xavier Durando

59 Efficacy of Antiresorptive Drugs on Bone Mineral Density in Post-Menopausal Women With Early Breast Cancer Receiving Adjuvant Aromatase Inhibitors: A Systematic Review of Randomized Controlled Trials
Alessandro de Sire, Lorenzo Lippi, Konstantinos Venetis, Stefania Morganti, Elham Sajjadi, Claudio Curci, Antonio Ammendolia, Carmen Criscitiello, Nicola Fusco and Marco Invernizzi

76 Effect of Supervised Resistance Training on Arm Volume, Quality of Life and Physical Perfomance Among Women at High Risk for Breast Cancer-Related Lymphedema: A Study Protocol for a Randomized Controlled Trial (STRONG-B)
Karol Ramírez-Parada, Maria Lopez-Garzon, Cesar Sanchez-Rojel, Militza Petric-Guajardo, Margarita Alfaro-Barra, Rodrigo Fernández-Verdejo, Alvaro Reyes-Ponce, Gina Merino-Pereira and Irene Cantarero-Villanueva

85 Feasibility for Using Thermography Throughout an Exercise Program in Mastectomized Patients
Maria Jane das Virgens Aquino, Paula Michele dos Santos Leite, Ingrid Kyelli Lima Rodrigues and Josimari Melo DeSantana

92 Establishing Minimal Clinically Important Differences for the Quality of Life Instrument in Patients With Breast Cancer QLICP-BR (V2.0) Based on Anchor-Based and Distribution-Based Methods
Fei Li, Yuxi Liu, Chonghua Wan, Jiali Zhou, Jianfeng Tan and Huanwei Chen

100 Long-Term Patient Satisfaction and Quality of Life Following Breast Reconstruction Using the BREAST-Q: A Prospective Cohort Study
Makoto Shiraishi, Yoshihiro Sowa, Itaru Tsuge, Takuya Kodama, Naoki Inafuku and Naoki Morimoto

109 Primary Neuroendocrine Tumor of the Breast: Current Understanding and Future Perspectives
Hongna Sun, Shuang Dai, Junnan Xu, Linan Liu, Jiaxing Yu and Tao Sun

119 Associations Between Serum Reproductive Hormone Concentrations and Hormonal Receptor Status Among Postmenopausal Chinese Women With Breast Cancer: An Observational Study
Chuner Jiang, Peng Wu, Xiangming He, Jianfen Ni, Xiaowen Ding, Xiaohong Xu, Fangzheng Wang and Dehong Zou

126 Analysis of the Risk Factors for Elevated D-Dimer Level After Breast Cancer Surgery: A Multicenter Study Based on Nursing Follow-Up Data
Yanqiu Wang, Xi Liang, Shujun Wang, Yuying Wang, Ling Qin, Danni Chen, Yanlin Jiang and Hao Zhang

131 Hot flushes and sweating, sleep problems, joint and muscular discomfort, and physical and mental exhaustion in breast cancer survivors during the first 24 months of tamoxifen therapy: a prospective observational study
Sumi Sung, Yul Ha Min, Seul Ki Park and Sae Byul Lee

140 Baduanjin's impact on quality of life and sleep quality in breast cancer survivors receiving aromatase inhibitor therapy: a randomized controlled trial
Jingwen Liao, Yanyu Chen, Li Cai, Kun Wang, Shenghui Wu, Lan Wu, Bixiao Song, Min Hu and Xiaohui Hou

149 A pilot study of cognitive behavioural therapy integrated with activity pacing for fatigued breast cancer patients undergoing chemotherapy in Ethiopia
Mikiyas Amare Getu, Changying Chen, Adamu Addissie, Edom Seife, Panpan Wang and Eva Johanna Kantelhardt

frontiers | Frontiers in Oncology

TYPE Editorial
PUBLISHED 14 February 2023
DOI 10.3389/fonc.2023.1118718



OPEN ACCESS

EDITED AND REVIEWED BY
Kara Britt,
Peter MacCallum Cancer Centre, Australia

*CORRESPONDENCE
Julio C. de la Torre-Montero
juliodelatorre@comillas.edu

SPECIALTY SECTION
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

RECEIVED 07 December 2022
ACCEPTED 25 January 2023
PUBLISHED 14 February 2023

CITATION
de la Torre-Montero JC, Casla-Barrio S, Herrero-López B and García-Saénz JÁ (2023) Editorial: Exercise, physical therapy, and wellbeing in breast cancer patients. *Front. Oncol.* 13:1118718. doi: 10.3389/fonc.2023.1118718



# Editorial: Exercise, physical therapy, and wellbeing in breast cancer patients

Julio C. de la Torre-Montero[1*], Soraya Casla-Barrio[1], Blanca Herrero-López[1,2] and José Ángel García-Saénz[3]

[1]Comillas Pontifical University, San Juan de Dios School of Nursing and Physical Therapy, Madrid, Spain, [2]Hospital Gregorio Marañón, Medical Oncology Department, Madrid, Spain, [3]Hospital Clínico San Carlos, Medical Oncology Department, Madrid, Spain

KEYWORDS

**breast cancer, cares, well - being, physical exercice, physical therapy**

Editorial on the Research Topic
Exercise, physical therapy and wellbeing in breast cancer patients

Cancer diagnoses pose a risk of disease and a challenge for the health system: on the one hand, it is estimated that by 2040 the number of new diagnoses will increase by more than 53%, and on the other hand, in addition to the need for treatments, we have to respond in the form of treatments, which are not only limited to medical treatments or based on pharmacotherapy or radiotherapy, but also include interventions based on nutrition, physical exercise and other motivational interventions from the perspective of psychology and the modification of environmental factors, in addition to the comprehensive care of patients that includes the detoxification of noxious habits, and attention to sexuality (1). In most of this new paradigm of patient care, the family group, and interpersonal relationships play an important role in terms of the changes that must occur in the long term.

Adherence to treatment in these cases is not based on the patient's motivation to continue pharmacological treatment. Still, it is sometimes based on a change in routines, life habits, and the acquisition of new ones, which include attitude changes, and sometimes result in a decreased need for oral treatments. Body composition in long-term breast cancer survivors taking aromatase inhibitors is improved by aerobic exercise and resistance exercise, in addition to alleviating negative side effects, and patient reports outcomes are also improved (2).

This Research Topic asks, how does the type of well-being recovery program influence the intervention approach is taken, and which type of activity is most effective and adequate for each patient? This special issue brings together three study protocols, two systematic reviews, and one literature review, as well as nine original studies, four of which have a clinical trial design, five are observational studies, and one of which presents questionnaire validation of the quality of life.

Breast cancer, as well as the rest of the oncological diagnoses, presents a challenge, due to its great survival and the possibility of maintaining daily life activities with a high level of well-being and quality of life. Actions aimed at maintaining this quality of life, as well as solving present or potential problems are covered from a multidisciplinary perspective: oncologists, specialist nurses, social workers, physiotherapists, and experts in physical exercise and cancer, in addition to many others. Including patients in primary and

secondary prevention and treatment policies as front-line actors ensure they are active in their total recovery. There is already evidence regarding the prevention of breast cancer: some studies show that large cohorts of the population, regarding usual recommendations on physical exercise, lower the risk by 6-10% on those individuals that perform physical activity ranging from 7.5 to 15 MET [the metabolic equivalent of task] per week (3, 4).

One of the most worrying effects for clinicians and patients is usually lymphedema, especially treated from physiotherapy, where, with adequate training, it is expected to reduce the volume of the affected arm, as well as improve quality of life, the strength of grip and resistance in physical exercise performance. The protocol includes moderate to intense exercise sessions, following a specific upper and lower body work plan. (Ramírez-Parada et al.).

Common and known effects derived from post-chemotherapy oral treatments, such as those based on tamoxifen, show that more than 70% of patients show derived symptoms, especially if they are under 40 years of age. Anticipating this type of situation makes it much easier for symptoms to be controlled early and for measures to be taken to mitigate and minimize them (Sung et al.). On the other hand, the importance of behavioral therapies in terms of intrinsic motivation is highlighted to minimize the effects of one of the usual symptoms, such as fatigue, reaching a reduction of this symptom in 77.77% of patients from the start of the intervention until six weeks later. Also, of great importance, the reduction of depressive symptoms was reduced in 55.55% of the study participants (Getu et al.).

Breast tumors have different heterogeneities and one of the less common diagnoses is a neuroendocrine tumor of mammary location (Sun et al). The identification of biological markers that allow responding to less frequent diagnoses is presented as a challenge for researchers, especially when the inhibition of immune control points is not presented as the ideal treatment in these situations, in addition to the fact that chemotherapy is not always effective.

The bone health of patients undergoing hormonal treatment always represents a challenge in the long-term follow-up of patients who are under the effects of the different existing aromatase inhibitor treatments for their diagnosis. Zoledronic acid and Denosumab are the best options in bone resorption and what happens to these patients over time remains to be determined, as well as what aspects could be improved with specific plans for physical exercise, diet, and vitamin D supplementation (Sire et al.). Along the same lines, another systematic review that analyzes the effects of physical exercise and acupuncture shows that the effects of these treatments can minimize pain, in the case of acupuncture, and physical exercise significantly improves activities. of daily life. Secondly, other symptoms such as anxiety, lack of sleep, or fatigue do not present statistically significant improvements (Zhu et al.). Baduanjin is a form of qigong, with eight movements. The purpose of this series of movements is to increase internal energy through exercise and spiritual practice to improve health and fitness. The movements must be executed in a moderate, relaxed, fluid, and consistent manner. The force is only necessary for an instant, when changing movements, maintaining relaxation for the rest of the time. This type of training in 12 weeks could reduce Aromatase Inhibitor side effects: global quality of life and physical functioning scores increased significantly by 12.39 ($P < 0.001$) and 8.48 ($P < 0.001$) in the Baduanjin exercise group compared with those in the control group (Liao et al.).

Continuing with the understanding of the different clinical situations that may arise, the study of reproductive hormones, through the measurement of serum levels of reproductive hormones: luteinizing hormone (LH), E2, P, testosterone (T), follicle-stimulating hormone (FSH), and prolactin (PRL) in postmenopausal patients with breast cancer. The expression levels of ER, PR, HER2, and p53 were also determined. The relationships between these receptors and hormones were evaluated in 352 Breast Cancer patients. The results point out that postmenopausal-mediated decreases in serum LH and FSH levels were associated with increased ER and PR expression and decreased HER2 expression (Jiang et al.).

One study analyzed aspects of quality of life and long-term satisfaction in a cohort of 141 patients after reconstruction after breast cancer surgery. The results show that, compared to mastectomy without reconstruction, the latter offers better results for the well-being of patients after the diagnosis of breast cancer. Evaluated at one year and after five years, the best quality of life was evidenced, as well as a better state of well-being in those with psychiatric medication records in their medical history. (Shiraishi et al.).

One of the studies published in this special series analyzes the D-dimer values in the postoperative period of breast cancer surgery and thirteen clinicopathological factors, which were identified and included in the analysis. The distribution of several of these factors between the two groups (pre and postoperative D-dimer levels) was compared. Factors with significantly different distributions between the two groups were identified as potential risk factors for D-dimer variation. The high risk is revealed in patients with a history of diabetes, with complications such as thrombosis. Priority must be paid to preoperative tests to anticipate possible health complications (Wang et al.).

Two studies thoroughly analyze aspects related to physical exercise, of Physical Activity, Fitness, Body Composition, Immunological Biomarkers, and Psychological Parameters During the First Year After Diagnosis in Women with Non-Metastatic Breast Cancer, and the Association of Insomnia, Depressive Disorders, and Mood Disorders as Risk Factors in the general population. The first is a Study Protocol that will quantify daily physical activity and cardiorespiratory fitness in objective measurements in the context of cancer therapy for 12 months after diagnosis. Relationships between exercise, immune status, physical and psychoemotional outcomes, and the clinical course will be studied (Zemlin et al.). The second analyzes a retrospective cohort of 232,108 women diagnosed with insomnia, depressive disorders, and mood disorders. Women with insomnia and hyperlipidemia was associated with an increased risk rate for breast cancer. Insomnia together with the sleeping medication did not produce any more risks than each one alone. Contrary to what is sometimes thought by the common opinion, mood disorders did not appear to be associated with breast cancer diagnosis (Liu et al.).

One of the topics always presented as an area for improvement in research methodology is the statistical analysis methods used to assess the effectiveness of a quality-of-life test. Whether the results of this type of questionnaire are valid in clinical practice, the results of the validation by the Anchor method are presented as an additional solution, offered in the research (Li et al.). The relationship between quality of life and physical activity is already unquestionable. The

early physical activity proposed in the APACAN-2 protocol may offer results that improve those interventions that work with patients after the completion of adjuvant therapy (Ginzac et al.). New methods used in diagnosis and therapy are promising and have prospects for future development: surface thermography can be a very good option to monitor rehabilitation programs after mastectomy (Aquino et al.) without adverse effects, offering useful and interesting information for professionals.

Personalized physiotherapy programs, nutritional plans, cognitive interventions, and physical exercise are fundamental not only in nursing care, medical, pharmacological, or radiotherapy treatment. Still, they must go further and integrate each of the aspects that influence the quality of life and well-being of people, patients and their families.

## Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

## Acknowledgments

We would like to acknowledge our institution's efforts to promote research.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## References

1. Wilson BE, Jacob S, Yap ML, Ferlay J, Bray F, Barton MB. Estimates of global chemotherapy demands and corresponding physician workforce requirements for 2018 and 2040: A population-based study. *Lancet Oncol* (2019) 20(6):769–80. doi: 10.1016/S1470-2045(19)30163-9

2. Thomas GA, Cartmel B, Harrigan M, Fiellin M, Capozza S, Zhou Y, et al. The effect of exercise on body composition and bone mineral density in breast cancer survivors taking aromatase inhibitors. *Obes (Silver Spring)* (2017) 25(2):346–51. doi: 10.1002/oby.21729

3. Matthews CE, Moore SC, Arem H, Cook B, Trabert B, Håkansson N, et al. Amount and intensity of leisure-time physical activity and lower cancer risk. *J Clin Oncol* (2020) 38(7):686–97. doi: 10.1200/JCO.19.02407

4. Ainsworth BE, Haskell WL, Herrmann SD, Meckes NB, Tudor-Locke DR Jr, Greer C, et al. Compendium of physical activities: A second update of codes and MET values. *Med Sci Sports Exerc* (2011) 43(8):1575–81. doi: 10.1249/MSS.0b013e31821ece12

frontiers in Oncology

ORIGINAL RESEARCH
published: 11 October 2021
doi: 10.3389/fonc.2021.757626

# Association of Insomnia, Depressive Disorders, and Mood Disorders as Risk Factors With Breast Cancer: A Nationwide Population-Based Cohort Study of 232,108 Women in Taiwan

*Hui-Pu Liu*[1†], *James Cheng-Chung Wei*[2,3,4†], *Hei-Tung Yip*[5] *and Ming-Hsin Yeh*[3,6*]

[1] Department of General Surgery, Kaohsiung Armed Forces General Hospital, Kaohsiung, Taiwan, [2] Department of Allergy, Immunology & Rheumatology, Chung Shan Medical University Hospital, Taichung, Taiwan, [3] Institute of Medicine, College of Medicine, Chung Shan Medical University, Taichung, Taiwan, [4] Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan, [5] Management Office for Health Data, Clinical Trial Research Center, China Medical University Hospital, Taichung, Taiwan, [6] Department of Surgery, Chung Shan Medical University Hospital, Taichung, Taiwan

OPEN ACCESS

**Edited by:**
*Antonino Musolino, University of Parma, Italy*

**Reviewed by:**
*Marco Invernizzi, University of Eastern Piedmont, Italy*
*Laura Cortesi, University Hospital of Modena, Italy*

***Correspondence:**
*Ming-Hsin Yeh*
*breast5321@gmail.com*

[†]*These authors have contributed equally to this work*

**Specialty section:**
*This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology*

**Received:** *12 August 2021*
**Accepted:** *20 September 2021*
**Published:** *11 October 2021*

**Citation:**
*Liu H-P, Wei JC-C, Yip H-T and Yeh M-H (2021) Association of Insomnia, Depressive Disorders, and Mood Disorders as Risk Factors With Breast Cancer: A Nationwide Population-Based Cohort Study of 232,108 Women in Taiwan. Front. Oncol. 11:757626. doi: 10.3389/fonc.2021.757626*

**Background:** Insomnia, depressive disorders, and to a more general view, mood disorders are raising people's concerns and causing disability of life. Herein, we try to seek the association of such illnesses with subsequent breast cancer.

**Methods:** This population-based, retrospective cohort study used data from the Taiwan National Health Insurance Research Database. This study included 232,108 women diagnosed with insomnia, depressive disorders, and mood disorders from January 1, 2000 to December 31, 2013. Physician diagnosed insomnia, depressive disorders, or mood disorders using outpatient and inpatient records before diagnosis of breast cancer. Cox proportional hazards regression analysis is adjusted for women with insomnia, depressive disorders, mood disorders, and other factors like insured amount, urbanization, and comorbidities such as having subsequent breast cancer.

**Results:** Sleep medication was associated with a significantly increased incidence rate of breast cancer (aHR = 1.23 (95% CI = 1.13, 1.35), $p < 0.001$). Insomnia was associated with significant increased hazard of breast cancer (aHR = 1.16 (95% CI = 1.07, 1.27), $p < 0.001$). Annual insured amount >20,000 (TWD), high urbanization area, and hyperlipidemia were associated with increased hazard of breast cancer (aHR = 1.13 (95% CI = 1.01, 1.27), $p = 0.04$; aHR = 1.41 (95% CI = 1.17, 1.71), $p < 0.001$; aHR = 1.14 995% CI = 1.02, 1.29), $p = 0.02$, respectively). There was a positive correlation between depressive disorders and increased incidence rate of breast cancer but not statistically significant (aHR = 1.11 (95% CI = 0.99, 1.25), $p = 0.08$). Mood disorders were not associated with increased hazard (aHR = 1.11 (95% CI = 0.91, 1.34), $p = 0.31$).

**Conclusion:** In this study, women with insomnia had increased risk of breast cancer, particularly those in high urbanization or with high insured amounts. Sleep medication (benzodiazepine (BZD) or non-BZD) and hyperlipidemia were independently associated with a higher hazard ratio of breast cancer. Insomnia along with sleep medication did not yield more hazards than each alone. Mood disorders appeared to be not associated with subsequent breast cancer. However, depressive disorders, the subgroups of mood disorders, could possibly increase the incidence rate of breast cancer though not statistically significant.

**Keywords: breast cancer, depressive disorders, mood disorders, insomnia, sleeping medication, hyperlipidemia**

## INTRODUCTION

Breast cancer, the leading cause of cancer death in women, is drawing more and more attention in health issues universally. There are more than 2 million women with newly diagnosed breast cancer every year globally (1). In Taiwan, 13,965 new cases of breast cancer have been reported in 2017, being the most commonly diagnosed cancer in women: it can be estimated that nearly 27% of cancer cases in women is represented by breast cancer. Breast cancer is the most frequently diagnosed cancer and second most common cause of cancer death in the USA (2), and it is the principal cause of death in women aged 40 to 49 years; in this period, women are in transition of perimenopause and menopause.

Women may experience sleep disturbance, depression, and anxiety during perimenopause and menopause transition due to physiologic changes in responsiveness to gonadotropins with wide variation of hormone level (3). In the late perimenopausal transition lasting 1 to 3 years, most women will encounter amenorrhea for longer than 2 months and often suffer from vasomotor symptoms; during this period and early menopause, FSH level continue to rise while estradiol (E2) level is declining. It is not until 2 years after menopause that the hormone levels remain steady (4). These symptoms due to estrogen decline raise our concern for women's health about mental illness.

Impairment of cognitive function and affective function after diagnosis of breast cancer were reported (5), and alteration of hippocampus like deformation or volume loss were also found after major types of treatments. Some pivotal studies aimed at the survivorship of returning the quality of life to the status before diagnosis or even better (6). Breast cancer experience could have an impact on physical and psychosocial alterations such as increased risk of depression, anxiety, and intrusive thought, especially in younger patients. Disruption of body image-related (hair loss, weight gain, aesthetics, etc.) distress could be alleviated *via* psychological intervention (7, 8). Breast cancer-related fatigue is also a major issue influencing quality of life, and some rehabilitation protocols like aerobic exercise could help (9). Several studies were focused on prevalence of mental illness during surgical intervention or medical treatment after diagnosing breast cancer since many cases of breast cancer are associated with physical disability and a poor quality of life after their breast cancer diagnosis with symptoms of fatigue, depression, and anxiety (10). However, herein, we focused on the association of insomnia, depressive disorders, or mood disorders with subsequent breast cancer in women.

Insomnia, one of the most common sleep disorders, affects approximately 6%–30% of the overall population (11–13). Emerging evidence suggests that insomnia is independently associated with psychiatric diseases (14), impaired health-related quality of life (15), and increased risks of hormone-related diseases (16) such as cancers (17).

The mood disorders are currently confined to disorders in which the mood is depressed or elevated. Mood disorders have once been interchangeably viewed as "affective disorder", a term which is still used frequently. Some studies have revealed that depressive disorders are related to substantial mortality, some comorbidities, and disabilities (18, 19).

Globally, around 10.7% of disability can be attributed to unipolar major depression. According to Joyce (20), unipolar major depression accounts for nearly 20% of disease burden in women aged 15 to 44 years old in developed countries. Therefore, we also investigated the association of some variants like insured amount, level of urbanization, and residential location in representatives of socioeconomic status, with breast cancer.

## METHODS

### Data Sources/Measurement

The Taiwan National Health Insurance Research Database (NHIRD) was established in 1995. The compulsory National Health Insurance program covered more than 99% of Taiwan residents, and their original claim data were stored in NHIRD. We utilized and analyzed the Longitudinal Health Insurance Data (LHID), which contains data of one million random selected insureds. The medical data included outpatient and inpatient records, the medication used, and treatment received. The identification number was encoded for protecting privacy problems. The diagnostic codes were recorded based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved by the ethical review board of the China Medical University Hospital [CMUH104-REC2-115(AR-4)].

## Study Cohort

In this study, we conducted three cohort studies which are shown in **Figure 1**. The first cohort was an insomnia cohort. Patients who were newly diagnosed with insomnia (ICD-9-CM codes 307.41, 307.42, 307.49, 780.50, 780.52, 780.55, 780.56, and 780.59) were the cases in this cohort. Those without insomnia were the controls. For the second cohort, the case cohort consisted of the patients with depressive disorders (ICD-9-CM codes 296.2, 296.3, 298.0, 300.4, 311, and V79.0) and the control cohort were patients never diagnosed with depressive disorders. The last cohort recruited patients with mood disorders (ICD-9-CM codes 296.0–296.7) as the case cohort and patients without mood disorders as the control cohort. The first diagnosis was the index date for case cohort and a random date between 2000 and 2012 was assigned to controls as the index date. The study period for all cohorts was 2000 to 2013. We excluded patients who were male, aged below 20 and diagnosed with breast cancer before the index date. Control patients were matched to case patients according to age, insured amount, urbanization level, residential location, and index year in a 1:1 ratio for the insomnia cohort and in 1:4 ratio for depressive disorder and mood disorder cohorts.

## Primary Outcome

Breast cancer (ICD-9-CM code 174) was the main outcome in this study. Patients who received the Major Illness or Injury Certificate of breast cancer were defined as the outcome. We followed up the participants from the index date to the development of breast cancer; withdraw from the NHI program or the end of the study, Dec. 31, 2013.

## Variables

Demographic variables included age, insured amount, urbanization, and residential location. Age was divided into four groups: 20–30 years old; 31–40 years old; 41–50 years old; and >50 years old. The related comorbidities included chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 491, 492, and 496), hypertension (HTN) (ICD-9-CM codes 401–405), diabetes mellitus (DM) (ICD-9-CM code 250), chronic kidney disease (CKD) (ICD-9-CM code 585), and hyperlipidemia (ICD-9-CM code 272). We also considered the use of sleeping pills potential confounders.

## Statistical Methods

The difference of the categorical variables and continuous variables in case cohort and the control cohort were expressed by standard mean difference (SMD). SMD of less than 0.1 means the difference can be neglected. The hazard ratio (HR) and 95% confidence interval (CI) were calculated by the Cox proportional model. The Kaplan-Meier method was applied to obtain the cumulative incidence curves and tested by the Log-rank test. All statistical analysis was performed by software SAS (version 9.4 for Windows; SAS Institute, Inc., Cary, NC, USA). A $p$-value of less than 0.05 was the statistically significant level.

# RESULTS

## Patient Characteristics

### With and Without Insomnia

Baseline characteristics of the 116,009 women with noninsomnia and 116,009 women with insomnia in this cohort (mean [SD] age: 47.8 [16.4] in noninsomnia group and 47.6 [15.7] in insomnia group) are provided in **Table 1**. The insured amount within 10,000–20,000 was predominant in noninsomnia [36%] and insomnia [38%]. Patients were mainly in highly urbanized areas in the noninsomnia (69,759 [60%]) and insomnia (70,372 [61%]) groups. The majority of patients (noninsomnia (52,296 [45%]) and insomnia (51,792 [45%])) resided in the northern area of Taiwan. Compared with patients with noninsomnia, those with insomnia had more comorbidities including COPD

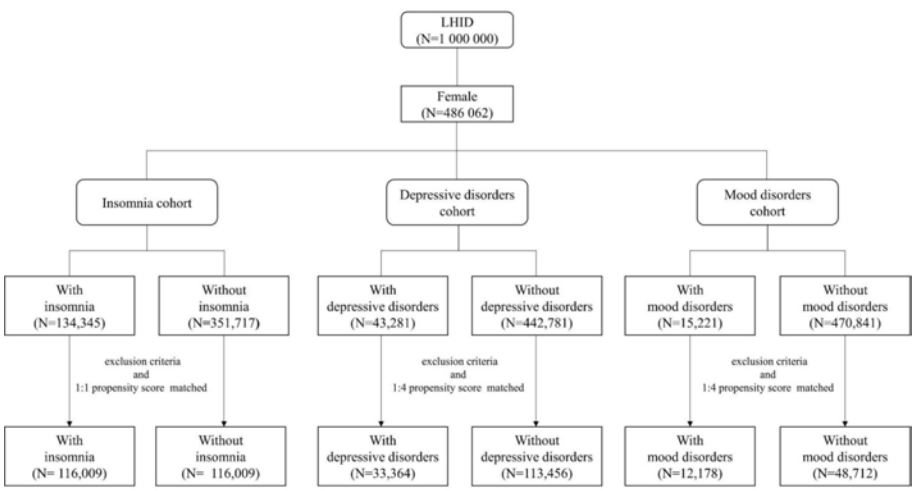



**FIGURE 1** | The flowchart of the three cohorts in this study: insomnia cohort, depressive disorder cohort, and mood disorder cohort.

**TABLE 1 |** The baseline characteristics of patients with and without insomnia.

| Variable | Noninsomnia | | Insomnia | | SMD |
|---|---|---|---|---|---|
| | *N* = 116,009 | | *N* = 116,009 | | |
| | *n* | % | *n* | % | |
| Age (year) | | | | | |
| 20–30 | 17,695 | 15% | 17,381 | 15% | 0.008 |
| 30–40 | 23,150 | 20% | 22,677 | 20% | 0.010 |
| 40–50 | 27,524 | 24% | 27,708 | 24% | 0.004 |
| >50 | 47,640 | 41% | 48,243 | 42% | 0.001 |
| Mean (SD) | 47.8 | (16.4) | 47.6 | (15.7) | 0.011 |
| Insured amount (TWD) | | | | | |
| ≤10,000 | 40,126 | 35% | 39,306 | 34% | 0.015 |
| 10,000–20,000 | 42,241 | 36% | 43,756 | 38% | 0.027 |
| >20,000 | 33,642 | 29% | 32,947 | 28% | 0.013 |
| Urbanization | | | | | |
| Low | 9,136 | 8% | 8,827 | 8% | 0.010 |
| Medium | 37,114 | 32% | 36,810 | 32% | 0.006 |
| High | 69,759 | 60% | 70,372 | 61% | 0.011 |
| Residential location | | | | | |
| Northern | 52,296 | 45% | 51,792 | 45% | 0.009 |
| Central | 28,835 | 25% | 31,369 | 27% | 0.050 |
| Southern | 13,846 | 12% | 12,882 | 11% | 0.026 |
| Eastern | 20,790 | 18% | 19,792 | 17% | 0.023 |
| Others | 242 | 0.21% | 174 | 0.15% | 0.014 |
| Comorbidities | | | | | |
| COPD | 18,879 | 16% | 28,271 | 24% | 0.202 |
| HTN | 24,046 | 21% | 30,609 | 26% | 0.134 |
| DM | 11,910 | 10% | 14,486 | 12% | 0.070 |
| CKD | 7,558 | 7% | 11,403 | 10% | 0.121 |
| Hyperlipidemia | 16,296 | 14% | 22,425 | 19% | 0.142 |
| Medication | | | | | |
| Sleep pills | 21,999 | 19% | 34,612 | 30% | 0.255 |

*COPD, chronic obstruction pulmonary disease; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; SMD, standard mean difference (less than 0.1 means no difference).*

**TABLE 2 |** The baseline characteristics of patients with and without depressive disorder.

| Variable | Nondepressive disorders | | Depressive disorders | | SMD |
|---|---|---|---|---|---|
| | *N* = 133,456 | | *N* = 33,364 | | |
| | *n* | % | *n* | % | |
| Age (year) | | | | | |
| 20–30 | 21,988 | 16% | 5,484 | 16% | 0.001 |
| 30–40 | 25,693 | 19% | 6,390 | 19% | 0.003 |
| 40–50 | 28,570 | 21% | 7,057 | 21% | 0.006 |
| >50 | 57,205 | 43% | 14,433 | 43% | 0.008 |
| Mean (SD) | 48.1 | (16.9) | 48.2 | (16.8) | 0.005 |
| Insured amount (TWD) | | | | | |
| ≤10,000 | 48,189 | 36% | 12,013 | 36% | 0.002 |
| 10,000–20,000 | 49,638 | 37% | 12,494 | 37% | 0.005 |
| >20,000 | 35,629 | 27% | 8,857 | 27% | 0.003 |
| Urbanization | | | | | |
| Low | 9,566 | 7% | 2,577 | 8% | 0.021 |
| Medium | 40,544 | 30% | 9,952 | 30% | 0.012 |
| High | 83,346 | 62% | 20,835 | 62% | <0.001 |
| Residential location | | | | | |
| Northern | 61,277 | 46% | 15,248 | 46% | 0.004 |
| Central | 30,909 | 23% | 7,700 | 23% | 0.002 |
| Southern | 15,474 | 12% | 3,886 | 12% | 0.002 |
| Eastern | 25,599 | 19% | 6,479 | 19% | 0.006 |
| Others | 197 | 0.15% | 51 | 0.15% | 0.001 |
| Comorbidities | | | | | |
| COPD | 25,314 | 19% | 9,200 | 28% | 0.205 |
| HTN | 31,182 | 23% | 10,350 | 31% | 0.173 |
| DM | 15,243 | 11% | 5,280 | 16% | 0.129 |
| CKD | 10,314 | 8% | 4,094 | 12% | 0.152 |
| Hyperlipidemia | 21,846 | 16% | 7,866 | 24% | 0.181 |
| Medication | | | | | |
| Sleep pills | 32,305 | 24% | 8,250 | 25% | 0.012 |

*COPD, chronic obstruction pulmonary disease; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; SMD, standard mean difference (less than 0.1 means no difference).*

(18,879 [16%] vs. 28,271 [24%]), HTN (24,046 [21%] vs. 30,609 [26%]), CKD (7,558 [7%] vs. 11,403 [10%]), and hyperlipidemia (16,296 [14%] vs. 22,425 [19%]) (SMD >0.1 for all). Compared with patients with noninsomnia, those with insomnia had more sleeping pills (21,999 [19%] vs. 34,612 [30%]) (SMD >0.1).

### With and Without Depressive Disorders

**Table 2** presents the baseline characteristics of 33,364 women with depressive disorders and 133,456 women without depressive disorders (mean [SD] age: 48.1 [16.9] in nondepressive disorder group and 48.2 [16.8] in depressive disorder group). Most patients were in highly urbanized areas (83,346 [62%]) for the control group and 20,835 [62%] for depressive disorders). Patients with depressive disorders had more comorbidities including COPD (25,314 [19%] vs. 9,200 [28%]), HTN (31,182 [23%] vs. 10,350 [31%]), DM (15,243 [11%] vs. 5,280 [16%]), CKD (10,314 [8%] vs. 4,094 [12%]), and hyperlipidemia (21,846 [16%] vs. 7,866 [24%]) (SMD >0.1) than those without depressive disorders.

### With and Without Mood Disorders

As shown in **Table 3**, 12,178 women with mood disorders and 48,712 patients without mood disorders (mean [SD] age: 46.6 [16.5%] in nonmood disorder group and 46.6 [16.4%] in depressive disorder group) are included. A higher proportion of comorbidities including COPD (9,165 [19%] vs. 3,480 [29%]), HTN (10,710 [22%] vs. 3,645 [30%]), DM (5,443 [11%] vs. 1,971 [16%]), CKD (3,661 [8%] vs. 1,519 [12%]), and hyperlipidemia (7,874 [16%] vs. 2,842 [23%]) were found in patient with mood disorders.

## The Incidence Rate and Hazard Ratios of Breast Cancer

### With and Without Insomnia

**Table 4** shows that women with insomnia had increased breast cancer (aHR = 1.16 (95% CI = 1.07, 1.27), $p < 0.001$). The cumulative incidence of breast cancer in patients with and without insomnia is shown in **Figure 2**. Patients with sleep medication were associated with a significantly increased incidence rate of breast cancer (aHR = 1.23 (95% CI = 1.13, 1.35), $p < 0.001$). Annual insured amount >20,000 (TWD), high urbanization area, and hyperlipidemia were associated with increased hazard of breast cancer (aHR = 1.13 (95% CI = 1.01, 1.27), $p = 0.04$; aHR = 1.41 (95% CI = 1.17, 1.71), $p < 0.001$; aHR = 1.14 (95% CI = 1.02, 1.29), $p = 0.02$, respectively).

**TABLE 3** | The baseline characteristics of patients with and without mood disorders.

| Variable | Nonmood disorders | | Mood disorders | | SMD |
|---|---|---|---|---|---|
| | *N* = 48,712 | | *N* = 12,178 | | |
| | *n* | % | *n* | % | |
| Age (year) | | | | | |
| 20–30 | 8,954 | 18% | 2,238 | 18% | <0.001 |
| 30–40 | 10,295 | 21% | 2,565 | 21% | 0.002 |
| 40–50 | 10,320 | 21% | 2,576 | 21% | 0.001 |
| >50 | 19,143 | 39% | 4,799 | 39% | 0.002 |
| Mean (SD) | 46.6 | (16.5) | 46.6 | (16.4) | 0.002 |
| Insured amount (TWD) | | | | | |
| ≤10,000 | 18,749 | 39% | 4,690 | 39% | <0.001 |
| 10,000–20,000 | 18,555 | 38% | 4,646 | 38% | 0.001 |
| >20,000 | 11,408 | 23% | 2,842 | 23% | 0.002 |
| Urbanization | | | | | |
| Low | 3,329 | 7% | 871 | 7% | 0.012 |
| Medium | 14,071 | 29% | 3,510 | 29% | 0.001 |
| High | 31,312 | 64% | 7,797 | 64% | 0.005 |
| Residential location | | | | | |
| Northern | 23,031 | 47% | 5,756 | 47% | <0.001 |
| Central | 10,815 | 22% | 2,700 | 22% | 0.001 |
| Southern | 4,901 | 10% | 1,225 | 10% | <0.001 |
| Eastern | 9,933 | 20% | 2,484 | 20% | <0.001 |
| Others | 32 | 0.07% | 13 | 0.11% | 0.014 |
| Comorbidities | | | | | |
| COPD | 9,165 | 19% | 3,480 | 29% | 0.231 |
| HTN | 10,710 | 22% | 3,645 | 30% | 0.182 |
| DM | 5,443 | 11% | 1,971 | 16% | 0.146 |
| CKD | 3,661 | 8% | 1,519 | 12% | 0.166 |
| Hyperlipidemia | 7,874 | 16% | 2,842 | 23% | 0.181 |
| Medication | | | | | |
| Sleep pills | 11,665 | 24% | 2,367 | 19% | 0.110 |

*COPD, chronic obstruction pulmonary disease; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; SMD, standard mean difference (less than 0.1 means no difference).*

### With and Without Depressive Disorders/Mood Disorders

The depressive disorder- or mood disorder-related incidence rates and hazard ratio of breast cancer are shown in **Tables 5** and **6**, respectively. In **Table 5**, there was a positive correlation between depressive disorders and increased incidence rate of breast cancer, but it was not statistically significant (aHR = 1.11 (95% CI = 0.99, 1.25), $p = 0.08$). Patients with sleep medication were associated with a significantly increased incidence rate of breast cancer (aHR = 1.39 (95% CI = 1.26, 1.54), $p < 0.001$). High urbanization area and hyperlipidemia were associated with increased hazard of breast cancer (aHR = 1.37 (95% CI = 1.10, 1.71), $p < 0.01$; aHR = 1.32 (95% CI = 1.15, 1.51), $p < 0.001$, respectively). In **Table 6**, the patients with mood disorders were not associated with increased hazard of breast cancer (aHR = 1.11 (95% CI = 0.91, 1.34), $p = 0.31$). Patients with sleep medication were associated with a significant increased incidence rate of breast cancer (aHR = 1.53 (95% CI = 1.30, 1.80), $p < 0.001$). Annual insured amount >20,000 (TWD) and hyperlipidemia were associated with increased hazard of breast cancer (aHR = 1.24 (95% CI = 1.00, 1.54), $p < 0.05$; aHR = 1.33 (95% CI = 1.06, 1.66), $p < 0.001$, respectively). Kaplan-Meier curves of breast cancer in the depressive disorder cohort and the mood disorder cohort are demonstrated in **Figures 3** and **4**, individually.

## The Association of Insomnia and Breast Cancer in Different Stratification

Patients with insomnia along with annual insured amount of more than 20,000 (TWD) (aHR = 1.27 (95% CI = 1.10, 1.46), $p < 0.001$) and high urbanization (aHR = 1.23 (95% CI = 1.11, 1.37), $p < 0.001$) were associated with significant increased hazard of breast cancer relative to those without insomnia, see **Table 7**. Insomnia patients with residential location in the northern area also increased the risk of breast cancer by 1.22 times (95% CI = 1.08, 1.38; $p = 0.001$) compared with the control patients who lived in the northern area. Patients who had insomnia with sleep medication did not yield an increased hazard of breast cancer over those without insomnia.

## The Effect of Sleeping Pills on Breast Cancer in Insomnia Cohort

The effect of sleeping pills on breast cancer is shown in **Table 8**. Either noninsomnia with sleeping pills (aHR = 1.46 (95% CI = 1.28, 1.67), $p < 0.001$), insomnia without sleeping pills (aHR = 1.28 (95% CI = 1.16, 1.42), $p < 0.001$), or insomnia with sleeping pills (aHR = 1.43 (95% CI = 1.27, 1.61), $p < 0.001$) was associated with significant increased hazard of breast cancer. However, insomnia combined with sleeping pills did not yield more hazard ratio than either insomnia or sleeping pills alone.

# DISCUSSION

To our knowledge, the present analysis, which pooled data from the Taiwan National Health Insurance Research Database, is the largest study to evaluate breast cancer and insomnia, depressive disorders, and mood disorders. In this cohort study, women (>20 years old) with insomnia had 16% higher rates of breast cancer. We also found that sleep medication, high insured amount, highly urbanized areas, and hyperlipidemia were associated with significantly increased incidence rate of breast cancer. There was a positive correlation between depressive disorders and increased incidence rate of breast cancer, but it was not statistically significant. Mood disorders were not associated with increased hazard of breast cancer. In summary, the risk factors of breast cancer in our study were insomnia, sleep medication, high urbanization, high insured amount, and hyperlipidemia.

Several studies concerning insomnia were mainly focused on the relationship of patients with preexisting breast cancer, but insomnia as a risk factor for breast cancer among primarily cancer-free women were rarely investigated (17, 21). Shift work involving circadian disruption was classified as being a probable carcinogen to humans according to the World Health Organization's International Agency for Research on Cancer in 2007 (22). The likely underlying mechanisms could be disturbed sleep, exposure to light at night, and other lifestyle factors (23–25). A positive correlation between circadian disruption and

**TABLE 4 |** The incidence rates and hazard ratios of breast cancer in insomnia cohort.

| Variable | Breast cancer | | | cHR (95% CI) | aHR[a] (95% CI) |
|---|---|---|---|---|---|
| | n | PY | IR | | |
| Insomnia | | | | | |
| No | 1,023 | 874,576 | 1.17 | 1.00 (–) | 1.00 (–) |
| Yes | 1,257 | 892,053 | 1.41 | 1.21 (1.12, 1.32)*** | 1.16 (1.07, 1.27)*** |
| Age (year) | | | | | |
| 20–30 | 47 | 257,668 | 0.18 | 1.00 (–) | 1.00 (–) |
| 30–40 | 339 | 354,040 | 0.96 | 5.16 (3.80, 7.00)*** | 4.80 (3.52, 6.54)*** |
| 40–50 | 801 | 446,414 | 1.79 | 9.57 (7.13, 12.8)*** | 8.64 (6.39, 11.7)*** |
| >50 | 1,093 | 708,507 | 1.54 | 8.28 (6.18, 11.1)*** | 7.55 (5.59, 10.2)*** |
| Insured amount (TWD) | | | | | |
| ≤10,000 | 489 | 554,518 | 0.88 | 1.00 (–) | 1.00 (–) |
| 10,000–20,000 | 970 | 678,151 | 1.43 | 1.58 (1.42, 1.76)*** | 1.10 (0.99, 1.23) |
| >20,000 | 821 | 533,960 | 1.54 | 1.68 (1.50, 1.88)*** | 1.13 (1.01, 1.27)* |
| Urbanization | | | | | |
| Low | 130 | 139,811 | 0.93 | 1.00 (–) | 1.00 (–) |
| Medium | 678 | 565,687 | 1.20 | 1.31 (1.09, 1.59)** | 1.27 (1.05, 1.54)* |
| High | 1,472 | 1,061,131 | 1.39 | 1.52 (1.27, 1.82)*** | 1.41 (1.17, 1.71)*** |
| Residential location | | | | | |
| Northern | 1,122 | 790,556 | 1.42 | 1.00 (–) | 1.00 (–) |
| Central | 554 | 463,092 | 1.20 | 0.84 (0.76, 0.93)** | 0.95 (0.85, 1.06) |
| Southern | 254 | 200,251 | 1.27 | 0.89 (0.78, 1.02) | 0.96 (0.84, 1.11) |
| Eastern | 348 | 309,410 | 1.12 | 0.79 (0.70, 0.89)*** | 0.86 (0.76, 0.97)* |
| Others | 2 | 3,320 | 0.60 | 0.42 (0.10, 1.68) | 0.57 (0.14, 2.33) |
| Comorbidities | | | | | |
| COPD | | | | | |
| No | 1,819 | 1,432,028 | 1.27 | 1.00 (–) | |
| Yes | 461 | 334,601 | 1.38 | 1.10 (1.00, 1.22) | |
| HTN | | | | | |
| No | 1,676 | 1,373,140 | 1.22 | 1.00 (–) | 1.00 (–) |
| Yes | 604 | 393,490 | 1.53 | 1.27 (1.16, 1.39)*** | 0.96 (0.86, 1.07) |
| DM | | | | | |
| No | 1,991 | 1,581,543 | 1.26 | 1.00 (–) | 1.00 (–) |
| Yes | 289 | 185,087 | 1.56 | 1.27 (1.12, 1.44)*** | 1.00 (0.88, 1.15) |
| CKD | | | | | |
| No | 2,096 | 1,626,558 | 1.29 | 1.00 (–) | |
| Yes | 184 | 140,072 | 1.31 | 1.02 (0.88, 1.19) | |
| Hyperlipidemia | | | | | |
| No | 1,826 | 1,493,915 | 1.22 | 1.00 (–) | 1.00 (–) |
| Yes | 454 | 272,715 | 1.66 | 1.40 (1.27, 1.56)*** | 1.14 (1.02, 1.29)* |
| Medication | | | | | |
| Sleep pills | | | | | |
| No | 1,446 | 1,243,629 | 1.16 | 1.00 (–) | 1.00 (–) |
| Yes | 834 | 523,001 | 1.59 | 1.28 (1.18, 1.4)*** | 1.23 (1.13, 1.35)*** |

*p-value <0.05; **p-value <0.01; ***p-value <0.001.

*PY, person-years; IR, incidence rate (per 1,000 person-years); cHR, crude hazard ratio; aHR, adjusted hazard ratio; COPD, chronic obstruction pulmonary disease; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease.*

[a]*Adjusted by age, insured amount, HTN, DM, hyperlipidemia, and sleep pills.*

breast cancer (HR = 1.14 (95% CI = 1.08, 1.21)) was proposed in a meta-analysis of 28 studies. Whereas, short sleep duration (<7 h/night) and dose-response association with sleep deficiency were not conclusive (26). Neither chronotype nor individual insomnia symptoms were strongly associated with breast cancer in evidence (27, 28). The relationship between insomnia and breast cancer could be understood *via* metabolic dysfunction as glucose homeostasis imbalance. Those with elevated blood glucose were related to decreased survival independent of comorbid diabetes mellitus (type 2) and body mass index (29, 30). According to Borniger et al., in a single nonmetastatic model of breast cancer, the underlying mechanism mediating cancer-associated metabolic changes and sleep disruption may be aberrant activity of wake-stabilizing hypocretin/orexin (HO) neuron (31).

Sleep medication, also called hypnotics, are mainly divided into benzodiazepines (BZDs) and nonbenzodiazepines (non-BZDs), and other miscellaneous types like gamma-aminobutyric acid agonist, melatonin receptor agonists, antihistamines, sedating antidepressant, and eugeroic drugs are not commonly administered (32). Both BZDs and non-BZDs (zolpidem, most widely used) were found with increased risk of cancers including breast cancer in two Taiwanese population-based cohort studies (33, 34). According to Iqbal et al. (34), it was provided based on epidemiological and bioinformatics analysis approaches that diazepam and zolpidem, but not alprazolam, might be

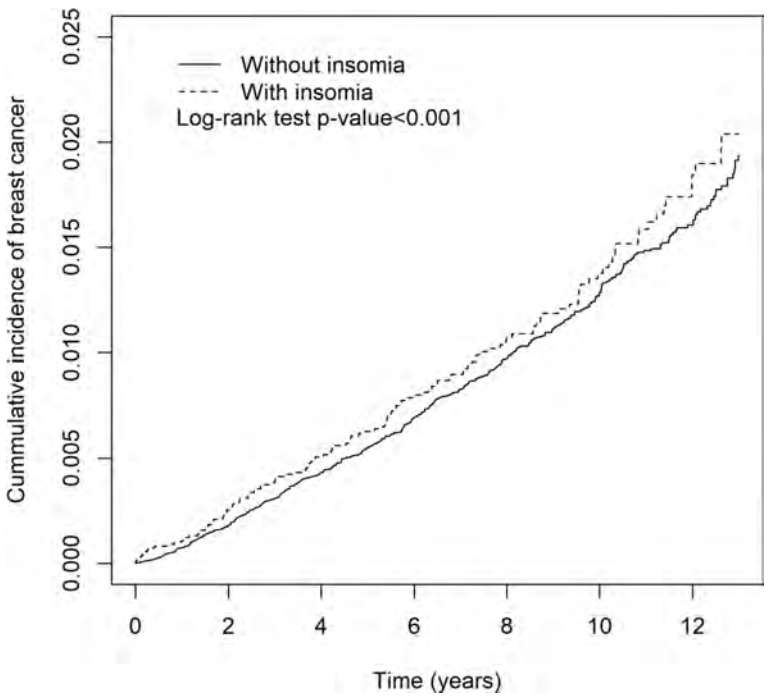



**FIGURE 2** | The cumulative incidence of breast cancer in patients with and without insomnia.

associated with breast cancer risk. The underlying mechanisms between sleep medication and cancer remain obscure. Overexpression of peripheral benzodiazepine receptors (PBR) due to BZDs has been implicated in breast cancer (35), and cell proliferation was found in some breast cancer cell lines after administration of PBR agonist (36). *In vitro* studies, non-BZDs as zopiclone, zaleplon, and ramelteon were found clastogenic, which can lead to carcinogenesis *via* the process of inducing disruption or breakages of chromosomes (37).

Depressive disorders, featured by sadness or irritability, are prevalent chronic diseases with psycho-physiological symptoms (38). In breast cancer patients with comorbid anxiety and depression, a tendency of diagnosis delay beyond 90 days from symptom identification was reported. Furthermore, treatment delay of longer than 60 days from diagnosis establishment was remarkable in those with severe mental illness (39). According to Chen et al. (40), curative surgery of breast cancer was associated with increased risk of subsequent depressive disorders, and those who developed depressive disorders had higher incidence rate of tumor recurrence and mortality when followed up. There are some probable underlying mechanisms suggesting depressive disorders being carcinogenic, such as impairing immune function, giving rise to aberrancy of the hypothalamic-pituitary-adrenal axis and inhibiting DNA repair (41–43). Nevertheless, in a meta-analysis of cohort study in 2007, based on seven heterogeneous studies, showed there was no significant association between depression and subsequent breast cancer risk (44). Another recent meta-analysis of cohort study derived from 11 cohort studies in 2015 showed epidemiological evidence was insufficient to support a positive association between depression and breast cancer (45). In our study, we found a positive correlation between depressive disorders and increased incidence rate of breast cancer, but it was not statistically significant.

Mood disorders are great disease entities that include depressive disorders and bipolar disorders. Mood disorders in the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (DSM-IV) have been replaced with multiple specifiers describing depressive disorders and bipolar disorders in the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* (DSM-V) (46). Also, DSM-IV entity of mood disorder NOS has been replaced with unspecified bipolar disorder and unspecified depressive disorder in DSM-V. To date, there were no previous studies aimed at the association between mood disorder and cancers. Since no remarkable association between bipolar disorders and breast cancer was noted in a nationwide cohort study (39), the association between depressive disorders and breast cancer was weak as mentioned above. It was hypothesized that mood disorders should be less coherent to breast cancer in that mood disorders are mainly partitioned into bipolar disorders and depressive disorders, and such inference was verified in our study, that is, mood disorders were not associated with increased hazard of breast cancer.

In high urbanization areas, in this study, the incidence rate of breast cancer in women was higher than in low urbanization areas. Also, a high insured amount was associated with increased breast cancer incidence. In a cohort study, high socioeconomic status and high income were found to have increased the incidence rate of breast cancer in the USA; however, income was not significantly correlated with mortality (47). In general, breast cancer has been regarded as a disease of affluence in risk

**TABLE 5 |** The incidence rates and hazard ratios of breast cancer in depressive disorder cohort.

| Variable | Breast cancer | | | cHR (95% CI) | aHR[a] (95% CI) |
|---|---|---|---|---|---|
| | n | PY | IR | | |
| Depressive disorders | | | | | |
| No | 1,308 | 1,042,122 | 1.26 | 1.00 (–) | 1.00 (–) |
| Yes | 360 | 257,472 | 1.40 | 1.12 (1.00, 1.26) | 1.11 (0.99, 1.25) |
| Age (year) | | | | | |
| 20–30 | 39 | 225,057 | 0.17 | 1.00 (–) | 1.00 (–) |
| 30–40 | 262 | 265,806 | 0.99 | 5.76 (4.1, 8.09)*** | 5.36 (3.79, 7.58)*** |
| 40–50 | 537 | 293,100 | 1.83 | 10.8 (7.79, 15.04)*** | 9.71 (6.93, 13.6)*** |
| >50 | 830 | 515,631 | 1.61 | 9.68 (6.99, 13.4)*** | 8.54 (6.10, 12.0)*** |
| Insured amount (TWD) | | | | | |
| ≤10,000 | 394 | 444,643 | 0.89 | 1.00 (–) | 1.00 (–) |
| 10,000–20,000 | 710 | 494,198 | 1.44 | 1.60 (1.42, 1.81)*** | 1.10 (0.97, 1.25) |
| >20,000 | 564 | 360,753 | 1.56 | 1.74 (1.53, 1.98)*** | 1.13 (0.99, 1.29) |
| Urbanization | | | | | |
| Low | 93 | 94,619 | 0.98 | 1.00 (–) | 1.00 (–) |
| Medium | 439 | 389,455 | 1.13 | 1.14 (0.91, 1.43) | 1.15 (0.92, 1.45) |
| High | 1,136 | 815,520 | 1.39 | 1.42 (1.15, 1.75)** | 1.37 (1.10, 1.71)** |
| Residential location | | | | | |
| Northern | 843 | 598,870 | 1.41 | 1.00 (–) | 1.00 (–) |
| Central | 353 | 301,025 | 1.17 | 0.82 (0.72, 0.93)** | 0.89 (0.78, 1.02) |
| Southern | 161 | 150,151 | 1.07 | 0.76 (0.64,0.9)** | 0.81 (0.68, 0.96)* |
| Eastern | 311 | 247,579 | 1.26 | 0.89 (0.79, 1.02) | 0.95 (0.83, 1.09) |
| Others | 0 | 1,970 | 0.00 | 0.00 (0, Inf) | |
| Comorbidities | | | | | |
| COPD | | | | | |
| No | 1,323 | 1,065,561 | 1.24 | 1.00 (–) | 1.00 (–) |
| Yes | 345 | 234,033 | 1.47 | 1.24 (1.1, 1.4)*** | 1.05 (0.92, 1.18) |
| HTN | | | | | |
| No | 1,204 | 1,017,375 | 1.18 | 1.00 (–) | 1.00 (–) |
| Yes | 464 | 282,219 | 1.64 | 1.44 (1.29, 1.6)*** | 1.02 (0.90, 1.16) |
| DM | | | | | |
| No | 1,466 | 1,164,932 | 1.26 | 1.00 (–) | 1.00 (–) |
| Yes | 202 | 134,662 | 1.50 | 1.24 (1.07, 1.44)** | 0.86 (0.73, 1.01) |
| CKD | | | | | |
| No | 1,511 | 1,199,194 | 1.26 | 1.00 (–) | 1.00 (–) |
| Yes | 157 | 100,400 | 1.56 | 1.27 (1.07, 1.49)** | 1.01 (0.85, 1.19) |
| Hyperlipidemia | | | | | |
| No | 1,307 | 1,102,930 | 1.19 | 1.00 (–) | 1.00 (–) |
| Yes | 361 | 196,664 | 1.84 | 1.63 (1.45, 1.83)*** | 1.32 (1.15, 1.51)*** |
| Medication | | | | | |
| Sleep pills | | | | | |
| No | 1,008 | 903,466 | 1.12 | 1.00 (–) | 1.00 (–) |
| Yes | 660 | 396,128 | 1.67 | 1.41 (1.28, 1.56)*** | 1.39 (1.26, 1.54)*** |

**p-value <0.05; **p-value <0.01; ***p-value <0.001.*

*PY, person-years; IR, incidence rate (per 1,000 person-years); cHR, crude hazard ratio; aHR, adjusted hazard ratio; COPD, chronic obstruction pulmonary disease; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease.*

[a]*Adjusted by age, insured amount, COPD, HTN, DM, CKD, hyperlipidemia, and sleep pills.*

factors such as delayed childbirth (48), less breastfeeding (49), and hormone supplements (50), which are more visible in affluent women. In one way, women in high socioeconomic areas have more accessibility to breast cancer screening as mammograms that detect more hidden cancer cases are highly available.

Hyperlipidemia is a status of chronic inflammation, which is a possible etiology contributing to breast cancer progression through activation of TLR signaling by oxidized LDL (51). In a hyperlipidemic mouse model, cholesterol and its metabolites have been verified to increase breast cell proliferation (52). In an observational study of 314 cases in China, elevated serum lipoprotein was associated with breast cancer (53). It is suggested that exercise could reduce the risk of hyperlipidemia-associated breast cancer *via* improving chronic inflammation, lowering blood lipid level, and exerting specific anticancer effects (54). In this study, we found that hyperlipidemia was an independent risk factor for breast cancer.

## STUDY LIMITATION

As this is a secondary analysis of observational data across the study period, we can only present the associations among breast

**TABLE 6 |** The incidence rates and hazard ratios of breast cancer in mood disorder cohort.

| Variable | Breast cancer | | | cHR (95% CI) | aHR[a] (95% CI) |
|---|---|---|---|---|---|
| | n | PY | IR | | |
| Mood disorders | | | | | |
| No | 495 | 375,364 | 1.32 | 1.00 (–) | 1.00 (–) |
| Yes | 131 | 91,702 | 1.43 | 1.09 (0.90, 1.32) | 1.11 (0.91,1.34) |
| Age (year) | | | | | |
| 20–30 | 14 | 90,695 | 0.15 | 1.00 (–) | 1.00 (–) |
| 30–40 | 129 | 104,577 | 1.23 | 7.86 (4.53, 13.7)*** | 7.30 (4.16,12.8)*** |
| 40–50 | 189 | 103,438 | 1.83 | 11.7 (6.81, 20.2)*** | 10.3 (5.92,18.0)*** |
| >50 | 294 | 168,356 | 1.75 | 11.5 (6.73, 19.7)*** | 9.72 (5.57, 16.9)*** |
| Insured amount (TWD) | | | | | |
| ≤10,000 | 153 | 171,782 | 0.89 | 1.00 (–) | 1.00 (–) |
| 10,000–20,000 | 261 | 179,997 | 1.45 | 1.61 (1.32, 1.96)*** | 1.08 (0.88, 1.32) |
| >20,000 | 212 | 115,288 | 1.84 | 2.01 (1.63, 2.47)*** | 1.24 (1.00, 1.54)* |
| Urbanization | | | | | |
| Low | 41 | 33,127 | 1.24 | 1.00 (–) | |
| Medium | 152 | 132,318 | 1.15 | 0.94 (0.66, 1.32) | |
| High | 433 | 301,621 | 1.44 | 1.17 (0.85, 1.61) | |
| Residential location | | | | | |
| Northern | 314 | 222,849 | 1.41 | 1.00 (–) | |
| Central | 139 | 102,413 | 1.36 | 0.97 (0.79, 1.18) | |
| Southern | 55 | 45,434 | 1.21 | 0.87 (0.65, 1.16) | |
| Eastern | 116 | 95,951 | 1.21 | 0.86 (0.69, 1.06) | |
| Others | 2 | 420 | 4.76 | 3.27 (0.81, 13.1) | |
| Comorbidities | | | | | |
| COPD | | | | | |
| No | 489 | 382,740 | 1.28 | 1.00 (–) | 1.00 (–) |
| Yes | 137 | 84,326 | 1.62 | 1.33 (1.1, 1.61)** | 1.11 (0.91, 1.35) |
| HTN | | | | | |
| No | 463 | 370,835 | 1.25 | 1.00 (–) | 1.00 (–) |
| Yes | 163 | 96,231 | 1.69 | 1.41 (1.18, 1.69)*** | 0.90 (0.73, 1.12) |
| DM | | | | | |
| No | 531 | 418,970 | 1.27 | 1.00 (–) | 1.00 (–) |
| Yes | 95 | 48,096 | 1.98 | 1.63 (1.31, 2.03)*** | 1.17 (0.91, 1.50) |
| CKD | | | | | |
| No | 569 | 431,056 | 1.32 | 1.00 (–) | |
| Yes | 57 | 36,010 | 1.58 | 1.22 (0.93, 1.60) | |
| Hyperlipidemia | | | | | |
| No | 486 | 397,676 | 1.22 | 1.00 (–) | 1.00 (–) |
| Yes | 140 | 69,390 | 2.02 | 1.74 (1.44, 2.10)*** | 1.33 (1.06, 1.66)* |
| Medication | | | | | |
| Sleep pills | | | | | |
| No | 379 | 331,365 | 1.14 | 1.00 (–) | 1.00 (–) |
| Yes | 247 | 135,701 | 1.82 | 1.50 (1.28, 1.77)*** | 1.53 (1.30, 1.80)*** |

*p-value <0.05; **p-value <0.01; ***p-value <0.001.

*PY, person-years; IR, incidence rate (per 1,000 person-years); cHR, crude hazard ratio; aHR, adjusted hazard ratio; COPD, chronic obstruction pulmonary disease; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease.*

[a]*Adjusted by age, insured amount, COPD, HTN, DM, hyperlipidemia, and sleep pills.*

cancer in Taiwanese women with insomnia, depressive disorders, mood disorders, sleep medication, insured amount, and hyperlipidemia. Also, we can only deduce cause and effect by showing that these associations are likely to be cohesive with a causal relationship between increased incidence of breast cancer and insomnia, sleep medication, high insured amount, highly urbanized areas, or hyperlipidemia. The results from this study, therefore, should be considered exploratory but preplanned and still need to be confirmed in subsequent clinical trials in the future. In this study, breast cancer, insomnia, depressive disorders, and mood disorders were based on ICD-9 codes which are replaced by ICD-10 codes currently. Because we focus on hypnotics in a general view instead of comparison of specific drugs, we could not differentiate the coefficient effect of different drugs. Routine mental illness screening is not popular in the Taiwan healthcare system. Besides, mental illnesses typically manifest years before people seek treatment (55); hence, the actual number of mental illness diagnosed before breast cancer could be underestimated, giving rise to inadequate interpretation of results.

## CONCLUSIONS

In this study, women with insomnia had increased risk of breast cancer, especially those in high urbanization or with high insured

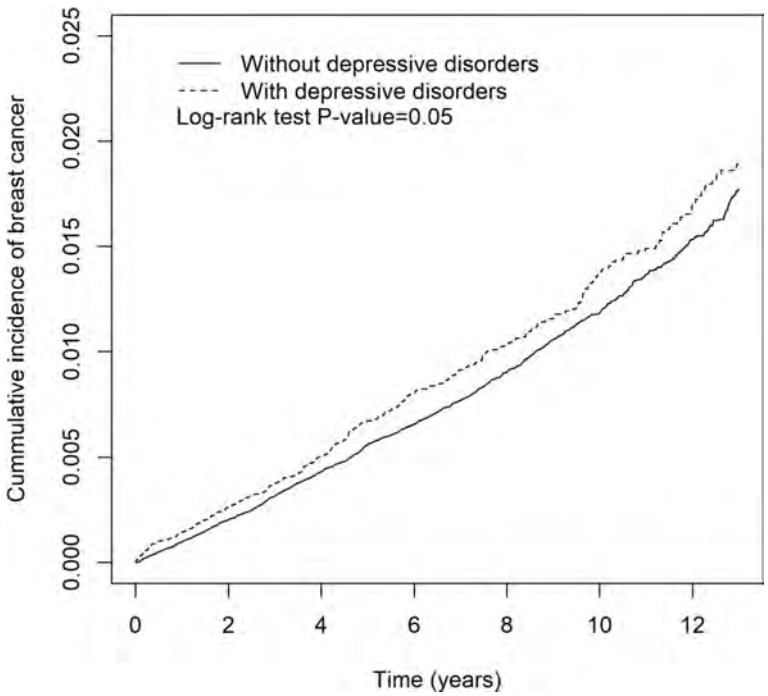



**FIGURE 3** | The cumulative incidence of breast cancer in patients with and without depressive disorders.

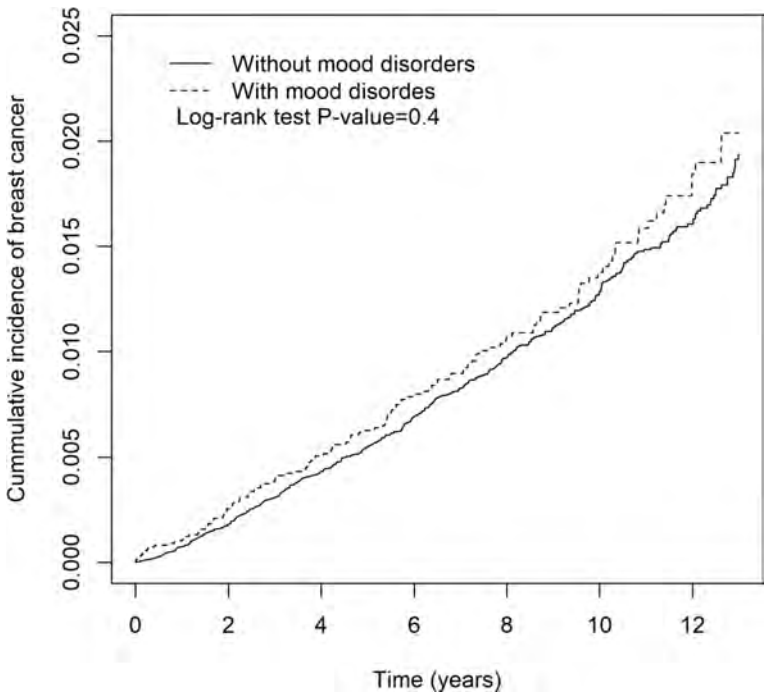



**FIGURE 4** | The cumulative incidence of breast cancer in patients with and without mood disorders.

**TABLE 7 |** The association of insomnia and breast cancer in different stratifications.

| Variable | Noninsomnia | | | Insomnia | | | cHR (95% CI) | aHR[a] (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | n | PY | IR | n | PY | IR | | |
| Age (year) | | | | | | | | |
| 20–30 | 24 | 130,189 | 0.18 | 23 | 127,479 | 0.18 | 1.05 (0.59, 1.87) | 1.12 (0.63, 2.01) |
| 30–40 | 147 | 179,431 | 0.82 | 192 | 174,609 | 1.10 | 1.37 (1.10, 1.70)** | 1.31 (1.05, 1.63)* |
| 40–50 | 372 | 223,081 | 1.67 | 429 | 223,334 | 1.92 | 1.16 (1.01, 1.33)* | 1.11 (0.84, 1.26) |
| >50 | 480 | 341,875 | 1.40 | 613 | 366,632 | 1.67 | 1.20 (1.06, 1.35)** | 1.17 (1.04, 1.32)* |
| Insured amount (TWD) | | | | | | | | |
| ≤10,000 | 228 | 277,420 | 0.82 | 261 | 277,098 | 0.94 | 1.15 (0.96, 1.37) | 1.10 (0.91, 1.31) |
| 10,000–20,000 | 434 | 328,620 | 1.32 | 536 | 349,531 | 1.53 | 1.16 (1.02, 1.32)* | 1.12 (0.98, 1,27) |
| >20,000 | 361 | 268,536 | 1.34 | 460 | 265,424 | 1.73 | 1.31 (1.14, 1.51)*** | 1.27 (1.10, 1.46)*** |
| Urbanization | | | | | | | | |
| Low | 50 | 69,996 | 0.71 | 80 | 69,815 | 1.15 | 1.69 (1.18, 2.41)** | 1.62 (1.12, 2.33)** |
| Medium | 336 | 280,454 | 1.20 | 342 | 285,233 | 1.20 | 1.00 (0.86, 1.16) | 0.96 (0.82, 1.12) |
| High | 637 | 524,126 | 1.22 | 835 | 537,005 | 1.55 | 1.29 (1.16, 1.43)*** | 1.23 (1.11, 1.37)*** |
| Residential location | | | | | | | | |
| Northern | 498 | 394,530 | 1.26 | 624 | 396,026 | 1.58 | 1.26 (1.12, 1.42)*** | 1.22 (1.08, 1.38)** |
| Central | 233 | 216,425 | 1.08 | 321 | 246,668 | 1.30 | 1.20 (1.01, 1.42)* | 1.14 (0.96, 1.35) |
| Southern | 117 | 103,864 | 1.13 | 137 | 96,387 | 1.42 | 1.30 (1.01, 1.66)* | 1.23 (0.95, 1.58) |
| Eastern | 173 | 157,823 | 1.10 | 175 | 151,587 | 1.15 | 1.07 (0.86, 1.32) | 1.00 (0.80, 1.23) |
| Others | 2 | 1,935 | 1.03 | 0 | 1,386 | 0.00 | | |
| Comorbidities | | | | | | | | |
| COPD | | | | | | | | |
| No | 864 | 749,752 | 1.15 | 955 | 682,276 | 1.40 | 1.22 (1.12, 1.34)*** | 1.17 (1.07, 1.29)*** |
| Yes | 159 | 124,824 | 1.27 | 302 | 209,777 | 1.44 | 1.12 (0.92, 1.35) | 1.12 (0.92, 1.36) |
| HTN | | | | | | | | |
| No | 794 | 713,200 | 1.11 | 882 | 659,939 | 1.34 | 1.21 (1.10, 1.34)*** | 1.18 (1.07, 1.30)*** |
| Yes | 229 | 161,376 | 1.42 | 375 | 232,114 | 1.62 | 1.13 (0.96, 1.34) | 1.11 (0.94, 1.31) |
| DM | | | | | | | | |
| No | 917 | 796,971 | 1.15 | 1,074 | 784,571 | 1.37 | 1.20 (1.10, 1.31)*** | 1.15 (1.05, 1.26)** |
| Yes | 106 | 77,605 | 1.37 | 183 | 107,482 | 1.70 | 1.21 (0.96, 1.54) | 1.20 (0.95, 1.53) |
| CKD | | | | | | | | |
| No | 963 | 823,377 | 1.17 | 1,133 | 803,181 | 1.41 | 1.22 (1.12, 1.33)*** | 1.17 (1.07, 1.28)*** |
| Yes | 60 | 51,200 | 1.17 | 124 | 88,872 | 1.40 | 1.19 (0.87, 1.62) | 1.16 (0.85, 1.59) |
| Hyperlipidemia | | | | | | | | |
| No | 860 | 766,579 | 1.12 | 966 | 727,336 | 1.33 | 1.20 (1.09, 1.31)*** | 1.16 (1.06, 1.28)** |
| Yes | 163 | 107,997 | 1.51 | 291 | 164,717 | 1.77 | 1.16 (0.95, 1.40) | 1.16 (0.96, 1.41) |
| Medication | | | | | | | | |
| Sleep pills | | | | | | | | |
| No | 682 | 666,869 | 1.02 | 764 | 576,760 | 1.32 | 1.31 (1.18, 1.45)*** | 1.27 (1.15, 1.42)*** |
| Yes | 341 | 207,707 | 1.64 | 493 | 315,293 | 1.56 | 0.97 (0.85, 1.12) | 0.97 (0.84, 1.11) |

**p-value <0.05; **p-value <0.01; ***p-value <0.001.*

*PY, person-years; IR, incidence rate (per 1,000 person-years); cHR, crude hazard ratio; aHR, adjusted hazard ratio; COPD, chronic obstruction pulmonary disease; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease.*

*[a]Adjusted by age, insured amount, hypertension, diabetes, hyperlipidemia, and sleep pills.*

**TABLE 8 |** The effect of sleep pills on breast cancer in insomnia cohort.

| Insomnia | Sleep pills | *N* | *n* | cHR (95% CI) | aHR[a] (95% CI) |
|---|---|---|---|---|---|
| No | No | 94,010 | 682 | 1.00 (–) | 1.00 (–) |
| No | Yes | 21,999 | 341 | 1.47 (1.29, 1.68)*** | 1.46 (1.28, 1.67)*** |
| Yes | No | 81,397 | 764 | 1.30 (1.18, 1.45)*** | 1.28 (1.16, 1.42)*** |
| Yes | Yes | 34,612 | 493 | 1.45 (1.29, 1.63)*** | 1.43 (1.27, 1.61)*** |

****p-value <0.001.*

*N, number of people; n, number of breast cancer; cHR, crude hazard ratio; aHR, adjusted hazard ratio. [a]Adjusted by age, insured amount, hypertension, diabetes, hyperlipidemia, and sleep pills.*

amounts. Sleep medication (BZD or non-BZD) and hyperlipidemia were independently associated with a higher hazard ratio of breast cancer. Insomnia combined with sleep medication did not yield more hazard as a synergic effect. Administration of sleeping pills should be less encouraged in women, if still needed, and they should be referred to a breast cancer department for regular screening, as are those diagnosed with insomnia. Mood disorders appeared to be not associated with subsequent breast cancer. However, depressive disorders, the subgroups of mood disorders, could possibly increase the

incidence rate of breast cancer though not statistically significant. These findings emphasize the importance of early screening of breast cancer for patients with possible risk factors. Future studies evaluating differences in breast tumor cell type, differentiation, and genotype may help target interventions.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the China Medical University Hospital [CMUH104-REC2-115(AR-4)]. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

Design: M-HY and JW. Acquisition of data: H-TY. Statistical analysis and interpretation: H-TY and H-PL. Manuscript writing: H-PL, JW, H-TY, and M-HY. All authors contributed to the article and approved the submitted version.

## ACKNOWLEDGMENTS

We thank the National Health Insurance Administration, Ministry of Health and Welfare, and National Health Research Institutes, Taiwan, for providing access to the National Health Insurance Research Database.

## REFERENCES

1. Heer E, Harper A, Escandor N, Sung H, McCormack V, Fidler-Benaoudia MM. Global Burden and Trends in Premenopausal and Postmenopausal Breast Cancer: A Population-Based Study. *Lancet Glob Health* (2020) 8(8): e1027–37. doi: 10.1016/S2214-109X(20)30215-1
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2020. *CA Cancer J Clin* (2020) 70(1):7–30. doi: 10.3322/caac.21590
3. Potter B, Schrager S, Dalby J, Torell E, Hampton A. Menopause. *Prim Care* (2018) 45(4):625–41. doi: 10.1016/j.pop.2018.08.001
4. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive Summary of the Stages of Reproductive Aging Workshop + 10: Addressing the Unfinished Agenda of Staging Reproductive Aging. *J Clin Endocrinol Metab* (2012) 97(4):1159–68. doi: 10.1210/jc.2011-3362
5. Duijts SF, van der Beek AJ, Boelhouwer IG, Schagen SB. Cancer-Related Cognitive Impairment and Patients' Ability to Work: A Current Perspective. *Curr Opin Support Palliat Care* (2017) 11(1):19–23. doi: 10.1097/SPC.0000000000000248
6. Invernizzi M, Kim J, Fusco N. Editorial: Quality of Life in Breast Cancer Patients and Survivors. *Front Oncol* (2020) 10:620574. doi: 10.3389/fonc.2020.620574
7. Sebri V, Durosini I, Triberti S, Pravettoni G. The Efficacy of Psychological Intervention on Body Image in Breast Cancer Patients and Survivors: A Systematic-Review and Meta-Analysis. *Front Psychol* (2021) 12:611954. doi: 10.3389/fpsyg.2021.611954
8. Nardin S, Mora E, Varughese FM, D'Avanzo F, Vachanaram AR, Rossi V, et al. Breast Cancer Survivorship, Quality of Life, and Late Toxicities. *Front Oncol* (2020) 10:864. doi: 10.3389/fonc.2020.00864
9. Invernizzi M, de Sire A, Lippi L, Venetis K, Sajjadi E, Gimigliano F, et al. Impact of Rehabilitation on Breast Cancer Related Fatigue: A Pilot Study. *Front Oncol* (2020) 10:556718. doi: 10.3389/fonc.2020.556718
10. Rogers LQ, Courneya KS, Anton PM, Verhulst S, Vicari SK, Robbs RS, et al. Effects of a Multicomponent Physical Activity Behavior Change Intervention on Fatigue, Anxiety, and Depressive Symptomatology in Breast Cancer Survivors: Randomized Trial. *Psychooncology* (2017) 26(11):1901–6. doi: 10.1002/pon.4254
11. Ohayon MM. Prevalence of DSM-IV Diagnostic Criteria of Insomnia: Distinguishing Insomnia Related to Mental Disorders From Sleep Disorders. *J Psychiatr Res* (1997) 31(3):333–46. doi: 10.1016/s0022-3956(97)00002-2
12. Ancoli-Israel S, Roth T. Characteristics of Insomnia in the United States: Results of the 1991 National Sleep Foundation Survey. I. *Sleep* (1999) 22(Suppl 2):S347–53.
13. National Institutes of Health. National Institutes of Health State of the Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults. *Sleep* (2005) 28):1049–57. doi: 10.1093/sleep/28.9.1049
14. Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, et al. Insomnia as a Predictor of Depression: A Meta-Analytic Evaluation of Longitudinal Epidemiological Studies. *J Affect Disord* (2011) 135(1-3):10–9. doi: 10.1016/j.jad.2011.01.011
15. Bolge SC, Doan JF, Kannan H, Baran RW. Association of Insomnia With Quality of Life, Work Productivity, and Activity Impairment. *Qual Life Res* (2009) 18(4):415–22. doi: 10.1007/s11136-009-9462-6
16. Vgontzas AN, Liao D, Bixler EO, Chrousos GP, Vela-Bueno A. Insomnia With Objective Short Sleep Duration Is Associated With a High Risk for Hypertension. *Sleep* (2009) 32(4):491–7. doi: 10.1093/sleep/32.4.491
17. Fang HF, Miao NF, Chen CD, Sithole T, Chung MH. Risk of Cancer in Patients With Insomnia, Parasomnia, and Obstructive Sleep Apnea: A Nationwide Nested Case-Control Study. *J Cancer* (2015) 6(11):1140–7. doi: 10.7150/jca.12490
18. Fann JR, Thomas-Rich AM, Katon WJ, Cowley D, Pepping M, McGregor BA, et al. Major Depression After Breast Cancer: A Review of Epidemiology and Treatment. *Gen Hosp Psychiatry* (2008) 30(2):112–26. doi: 10.1016/j.genhosppsych.2007.10.008
19. Phillips KA, Osborne RH, Giles GG, Dite GS, Apicella C, Hopper JL, et al. Psychosocial Factors and Survival of Young Women With Breast Cancer: A Population-Based Prospective Cohort Study. *J Clin Oncol* (2008) 26(28):4666–71. doi: 10.1200/JCO.2007.14.8718
20. Joyce PR. Epidemiology of Mood Disorders. In: *New Oxford Textbook of Psychiatry. 2 edn* ed. Oxford, UK: Oxford University Press (2012). pp. 645–50. doi: 10.1093/med/9780199696758.003.0086
21. Vogtmann E, Levitan EB, Hale L, Shikany JM, Shah NA, Endeshaw Y, et al. Association Between Sleep and Breast Cancer Incidence Among Postmenopausal Women in the Women's Health Initiative. *Sleep* (2013) 36(10):1437–44. doi: 10.5665/sleep.3032
22. Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of Shift-Work, Painting, and Fire-Fighting. *Lancet Oncol* (2007) 8(12):1065–6. doi: 10.1016/S1470-2045(07)70373-X
23. Stevens RG. Light-At-Night, Circadian Disruption and Breast Cancer: Assessment of Existing Evidence. *Int J Epidemiol* (2009) 38(4):963–70. doi: 10.1093/ije/dyp178
24. Fritschi L, Glass DC, Heyworth JS, Aronson K, Girschik J, Boyle T, et al. Hypotheses for Mechanisms Linking Shiftwork and Cancer. *Med Hypotheses* (2011) 77(3):430–6. doi: 10.1016/j.mehy.2011.06.002
25. Haus EL, Smolensky MH. Shift Work and Cancer Risk: Potential Mechanistic Roles of Circadian Disruption, Light at Night, and Sleep Deprivation. *Sleep Med Rev* (2013) 17(4):273–84. doi: 10.1016/j.smrv.2012.08.003

26. He C, Anand ST, Ebell MH, Vena JE, Robb SW. Circadian Disrupting Exposures and Breast Cancer Risk: A Meta-Analysis. *Int Arch Occup Environ Health* (2015) 88(5):533–47. doi: 10.1007/s00420-014-0986-x
27. Ramin C, Devore EE, Pierre-Paul J, Duffy JF, Hankinson SE, Schernhammer ES. Chronotype and Breast Cancer Risk in a Cohort of US Nurses. *Chronobiol Int* (2013) 30(9):1181–6. doi: 10.3109/07420528.2013.809359
28. Sen A, Opdahl S, Strand LB, Vatten LJ, Laugsand LE, Janszky I. Insomnia and the Risk of Breast Cancer: The HUNT Study. *Psychosom Med* (2017) 79 (4):461–8. doi: 10.1097/PSY.0000000000000417
29. Contiero P, Berrino F, Tagliabue G, Mastroianni A, Di Mauro MG, Fabiano S, et al. Fasting Blood Glucose and Long-Term Prognosis of non-Metastatic Breast Cancer: A Cohort Study. *Breast Cancer Res Treat* (2013) 138(3):951–9. doi: 10.1007/s10549-013-2519-9
30. Villarreal-Garza C, Shaw-Dulin R, Lara-Medina F, Bacon L, Rivera D, Urzua L, et al. Impact of Diabetes and Hyperglycemia on Survival in Advanced Breast Cancer Patients. *Exp Diabetes Res* (2012) 2012:732027. doi: 10.1155/2012/732027
31. Borniger JC, Walker Ii WH, Surbhi, Emmer KM, Zhang N, Zalenski AA, et al. A Role for Hypocretin/Orexin in Metabolic and Sleep Abnormalities in a Mouse Model of Non-Metastatic Breast Cancer. *Cell Metab* (2018) 28 (1):118–.e5. doi: 10.1016/j.cmet.2018.04.021
32. Kryger R, Wilce PA. The Effects of Alcoholism on the Human Basolateral Amygdala. *Neuroscience* (2010) 167(2):361–71. doi: 10.1016/j.neuroscience.2010.01.061
33. Kao CH, Sun LM, Liang JA, Chang SN, Sung FC, Muo CH. Relationship of Zolpidem and Cancer Risk: A Taiwanese Population-Based Cohort Study. *Mayo Clin Proc* (2012) 87(5):430–6. doi: 10.1016/j.mayocp.2012.02.012
34. Iqbal U, Nguyen PA, Syed-Abdul S, Yang HC, Huang CW, Jian WS, et al. Is Long-Term Use of Benzodiazepine a Risk for Cancer? *Med (Baltimore)* (2015) 94(6):e483. doi: 10.1097/MD.0000000000000483
35. Galiegue S, Casellas P, Kramar A, Tinel N, Simony-Lafontaine J. Immunohistochemical Assessment of the Peripheral Benzodiazepine Receptor in Breast Cancer and Its Relationship With Survival. *Clin Cancer Res* (2004) 10(6):2058–64. doi: 10.1158/1078-0432.ccr-03-0988
36. Akech J, Sinha Roy S, Das SK. Modulation of Cholinephosphotransferase Activity in Breast Cancer Cell Lines by Ro5-4864, a Peripheral Benzodiazepine Receptor Agonist. *Biochem Biophys Res Commun* (2005) 333(1):35–41. doi: 10.1016/j.bbrc.2005.05.071
37. Kripke DF. Hypnotic Drug Risks of Mortality, Infection, Depression, and Cancer: But Lack of Benefit. *F1000Res* (2016) 5:918. doi: 10.12688/f1000research.8729.3
38. Benson JR, Jatoi I, Keisch M, Esteva FJ, Makris A, Jordan VC. Early Breast Cancer. *Lancet* (2009) 373(9673):1463–79. doi: 10.1016/S0140-6736(09)60316-0
39. Iglay K, Santorelli ML, Hirshfield KM, Williams JM, Rhoads GG, Lin Y, et al. Diagnosis and Treatment Delays Among Elderly Breast Cancer Patients With Pre-Existing Mental Illness. *Breast Cancer Res Treat* (2017) 166(1):267–75. doi: 10.1007/s10549-017-4399-x
40. Chen SJ, Chang CH, Chen KC, Liu CY. Association Between Depressive Disorders and Risk of Breast Cancer Recurrence After Curative Surgery. *Med (Baltimore)* (2016) 95(33):e4547. doi: 10.1097/MD.0000000000004547
41. Kiecolt-Glaser JK, Robles TF, Heffner KL, Loving TJ, Glaser R. Psycho-Oncology and Cancer: Psychoneuroimmunology and Cancer. *Ann Oncol* (2002) 13(Suppl 4):165–9. doi: 10.1093/annonc/mdf655
42. Reiche EM, Morimoto HK, Nunes SM. Stress and Depression-Induced Immune Dysfunction: Implications for the Development and Progression of Cancer. *Int Rev Psychiatry* (2005) 17(6):515–27. doi: 10.1080/02646830500382102
43. Soygur H, Palaoglu O, Akarsu ES, Cankurtaran ES, Ozalp E, Turhan L, et al. Interleukin-6 Levels and HPA Axis Activation in Breast Cancer Patients With Major Depressive Disorder. *Prog Neuropsychopharmacol Biol Psychiatry* (2007) 31(6):1242–7. doi: 10.1016/j.pnpbp.2007.05.001
44. Oerlemans ME, van den Akker M, Schuurman AG, Kellen E, Buntinx F. A Meta-Analysis on Depression and Subsequent Cancer Risk. *Clin Pract Epidemiol Ment Health* (2007) 3:29. doi: 10.1186/1745-0179-3-29
45. Sun HL, Dong XX, Cong YJ, Gan Y, Deng J, Cao SY, et al. Depression and the Risk of Breast Cancer: A Meta-Analysis of Cohort Studies. *Asian Pac J Cancer Prev* (2015) 16(8):3233–9. doi: 10.7314/apjcp.2015.16.8.3233
46. Parker GF. DSM-5 and Psychotic and Mood Disorders. *J Am Acad Psychiatry Law* (2014) 42(2):182–90.
47. Lehrer S, Green S, Rosenzweig KE. Affluence and Breast Cancer. *Breast J* (2016) 22(5):564–7. doi: 10.1111/tbj.12630
48. Panagiotopoulou K, Katsouyanni K, Petridou E, Garas Y, Tzonou A, Trichopoulos D. Maternal Age, Parity, and Pregnancy Estrogens. *Cancer Causes Control* (1990) 1(2):119–24. doi: 10.1007/BF00053162
49. Freudenheim JL, Marshall JR, Graham S, Laughlin R, Vena JE, Bandera E, et al. Exposure to Breastmilk in Infancy and the Risk of Breast Cancer. *Epidemiology* (1994) 5(3):324–31. doi: 10.1097/00001648-199405000-00011
50. Chlebowski RT, Rohan TE, Manson JE, Aragaki AK, Kaunitz A, Stefanick ML, et al. Breast Cancer After Use of Estrogen Plus Progestin and Estrogen Alone: Analyses of Data From 2 Women's Health Initiative Randomized Clinical Trials. *JAMA Oncol* (2015) 1(3):296–305. doi: 10.1001/jamaoncol.2015.0494
51. Hovland A, Jonasson L, Garred P, Yndestad A, Aukrust P, Lappegard KT, et al. The Complement System and Toll-Like Receptors as Integrated Players in the Pathophysiology of Atherosclerosis. *Atherosclerosis* (2015) 241(2):480–94. doi: 10.1016/j.atherosclerosis.2015.05.038
52. Hwang S, Hartman IZ, Calhoun LN, Garland K, Young GA, Mitsche MA, et al. Contribution of Accelerated Degradation to Feedback Regulation of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase and Cholesterol Metabolism in the Liver. *J Biol Chem* (2016) 291(26):13479–94. doi: 10.1074/jbc.M116.728469
53. Xu J, Qiu X, Li Y, Sun N, Zhang Y, Shu J. Hyperlipoproteinemia (a) is Associated With Breast Cancer in a Han Chinese Population. *Med (Baltimore)* (2020) 99(38):e22037. doi: 10.1097/MD.0000000000022037
54. Buss LA, Dachs GU. The Role of Exercise and Hyperlipidaemia in Breast Cancer Progression. *Exerc Immunol Rev* (2018) 24:10–25.
55. Wang PS, Angermeyer M, Borges G, Bruffaerts R, Tat Chiu W, E. G. G D, et al. Delay and Failure in Treatment Seeking After First Onset of Mental Disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry* (2007) 6(3):177–85.


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

STUDY PROTOCOL
published: 19 October 2021
doi: 10.3389/fonc.2021.762709

# Longitudinal Assessment of Physical Activity, Fitness, Body Composition, Immunological Biomarkers, and Psychological Parameters During the First Year After Diagnosis in Women With Non-Metastatic Breast Cancer: The BEGYN Study Protocol

*Cosima Zemlin[1]*, Caroline Stuhlert[1], Julia Theresa Schleicher[1], Carolin Wörmann[1], Laura Altmayer[1], Marina Lang[1], Laura-Sophie Scherer[1], Ida Clara Thul[1], Carolin Müller[1], Elisabeth Kaiser[2], Regine Stutz[2], Sybelle Goedicke-Fritz[2], Laura Ketter[3], Michael Zemlin[2], Gudrun Wagenpfeil[4], Georges Steffgen[3] and Erich-Franz Solomayer[1]*

[1] Department for Gynecology, Obstetrics and Reproductive Medicine, Saarland University Medical Center, Homburg, Germany, [2] Department for General Pediatrics, Saarland University Medical Center, Homburg, Germany, [3] Department of Behavioural and Cognitive Sciences, Institute for Health and Behaviour, University of Luxembourg, Esch-sur-Alzette, Luxembourg, [4] Institute for Medical Biometry, Epidemiology and Medical Informatics (IMBEI), Saarland University, Homburg, Germany

OPEN ACCESS

**Edited by:**
Masakazu Toi,
Kyoto University, Japan

**Reviewed by:**
Alessandro de Sire,
University of Magna Graecia, Italy
Marco Invernizzi,
University of Eastern Piedmont, Italy

***Correspondence:**
Cosima Zemlin
cosima.zemlin@uks.eu

**Specialty section:**
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

**Received:** 22 August 2021
**Accepted:** 01 October 2021
**Published:** 19 October 2021

**Citation:**
Zemlin C, Stuhlert C, Schleicher JT, Wörmann C, Altmayer L, Lang M, Scherer L-S, Thul IC, Müller C, Kaiser E, Stutz R, Goedicke-Fritz S, Ketter L, Zemlin M, Wagenpfeil G, Steffgen G and Solomayer E-F (2021) Longitudinal Assessment of Physical Activity, Fitness, Body Composition, Immunological Biomarkers, and Psychological Parameters During the First Year After Diagnosis in Women With Non-Metastatic Breast Cancer: The BEGYN Study Protocol. Front. Oncol. 11:762709. doi: 10.3389/fonc.2021.762709

**Background:** Moderate physical activity is associated with an improved prognosis and psychosocial outcome in breast cancer patients. Although exercise and physical activity are associated with multiple physiological and psychological effects, many of the underlying mechanisms remain obscure. The BEGYN study (Influence of physical activity in breast cancer patients on physiological and psychological parameters and on biomarkers) aims at identifying potential associations between the extent of physical activity, fitness, body composition, immunological biomarkers, psycho-emotional parameters, and the course of treatment during the first year after diagnosis of breast cancer.

**Methods:** The prospective observational BEGYN study will include 110 non-metastatic breast cancer patients. The patients will be assessed during a base line visit prior to the initiation of the antineoplastic therapy and after 3, 6, 9 and 12 months. The physical activity will be measured using a fitness tracker and a self-assessment diary during the entire study. Each visit will include the assessment of (i) cardiorespiratory fitness measured by spiroergometry, (ii) body composition, (iii) psycho-emotional parameters (quality of life, mental health, fatigue, depression, distress, anxiety, well-being), and (iv) extensive blood tests including routine laboratory, vitamin D, selenium and immunologically relevant biomarkers (e.g., leukocyte subpopulations and cytokine profiles).

**Discussion:** Whereas most studies investigating the influence of physical activity in breast cancer patients focus on specific activities for three months or less, the BEGYN study will quantify the daily physical activity and cardiorespiratory fitness of breast cancer patients based on objective measurements in the context of the oncological therapy for 12 months after diagnosis. The study will reveal potential associations between exercise, immune status and physical as well as psycho-emotional outcome and the clinical course of the disease. Moreover, complementary therapies such as Vit D and Selenium supplementation and parameters investigating the motivation of the patients are part of the study. Due to this holistic approach, the BEGYN study will guide towards confirmatory studies on the role of physical activity in breast cancer patients to develop individualized counselling regarding the recommended type and extent of exercise.

**Trial Registration:** This study has been registered at the German Clinical Trials Register DRKS00024829.

**Keywords: breast cancer, physical activity, spiroergometry, psychological parameters, body composition, chemotherapy, immune monitoring, observational study**

## 1 INTRODUCTION

Historic recommendations to avoid physical activity during cancer treatment to save all energy for fighting the disease have proven wrong (1–6). Breast cancer is the most common cancer in women, accounting for more than 680.000 deaths per year worldwide (7). Although modern breast cancer treatment such as improved diagnostic and staging procedures, advanced systemic therapy, surgery and radiotherapy increases long-term survival and clinical outcome of breast cancer patients, there is still a deficiency of supportive and psychosocial care (8). Breast cancer survivors are at risk of suffering potentially disabling physical and psychological sequelae, such as lymphedema, axillary web syndrome, chronic pain, osteoporosis and fractures, arthralgia, chronic fatigue syndrome and depression (9). During and after antineoplastic therapy, rehabilitation and complementary therapies are crucial to improve the quality of life and overall prognosis of breast cancer survivors (10–12).

Multiple studies in cancer patients have demonstrated that physical activity and exercise correlate with an improved outcome regarding the course of the underlying disease and with a better tolerance to the antineoplastic treatments (13). For example, exercise had positive effects on the fatigue syndrome and quality of life in cancer (12, 14), the course of lymphedema (13, 15) and osteoporosis in breast cancer (16) and prostate cancer (17). Moreover, physical activity influences various functions of the immune system, such as the proportions of circulating leukocyte subsets and the expression of cytokines (4, 18–21). Moderate sporting activity has an immune-protective effect, whereas excessive sporting activity is associated with an increased susceptibility to infections - possibly mediated by a reduction in circulating natural killer cells (22). Natural killer cells and other leukocyte subsets play a crucial role in the physiological attempts of the organism to control cancer cells (23). Thus, Ashcraft et al. put forth the hypothesis that exercise-induced modulations of the immune status do not only alter the susceptibility to infections, but also the immune response to neoplastic diseases and the effectivity of antineoplastic therapies (24). Current data suggest that a complex interplay of the above-mentioned factors contributes to a positive correlation between the quantity of physical activities and event-free survival in cancer patients (69% reduced hazard of mortality among highly active patients) (25). In consequence, more prospective studies were recommended to characterize the influence of sporting activities on the immune system and on potential individualized rehabilitation approaches in cancer patients (9, 26, 27).

According to Mehnert et al. (28) the prevalence of any mental disorder among the major tumor entities is 32% and breast cancer has the highest prevalence of mental disorders with 42%. 17% of breast cancer patients are afflicted with anxiety disorders and 9% with affective disorders. Physical activity can affect anxiety and depression in breast cancer patients. Interestingly, leisure time physical activity was negatively related to depression, whereas occupational physical activity related positively to anxiety (29).

30% of disease-free breast cancer survivors suffer from cancer related fatigue syndrome, causing a massive reduction of psycho-emotional wellbeing and quality of life (30–32). Regular exercise plays an important role in the management of cancer-related fatigue (33–35). Clinical trials have shown that individual and patient-adapted exercise programs yield the best outcome regarding physical functioning and health among breast cancer patients (25, 32, 36–38).

The body composition strongly correlates with physical activity and is a relevant prognostic factor for breast cancer patients (39). On average, overweight patients have a higher risk to develop breast cancer, a higher rate of relapses and a shorter recurrence-free period (40). The loss of muscle mass and the gain of fat mass (sarcopenia) can be detected with a bioelectrical

impedance analysis, a simple, non-invasive technique (41). A lower muscle index can be associated with a higher toxicity of the chemotherapy (42).

Since the physical activity plays a key role in determining the prognosis of breast cancer patients, it is useful to combine exercise diaries with objective measurements such as pedometers or fitness trackers (43, 44). Moreover, this yields continuous information on vital parameters, including the pulse and resting heart rate as an estimate for overall cardiopulmonary fitness (45).

Studies that combine fitness tests, physical assessments, immunological markers, and psychological tests in breast cancer patients are still scarce, thus it is highly difficult to understand potential cross-links between these aspects. Filling this gap of knowledge could allow conclusions on individualized prevention and rehabilitation of the multiple sequelae that are potentially associated with breast cancer (9). Clinical studies in cancer patients must consider that according to current guidelines, all breast cancer patients are to be advised to exercise endurance and muscle strength (39). However, little is known on the extent to which patients adhere to this recommendation. Moreover, it would be unethical to withhold motivation for sportive activity from breast cancer patients for experimental purposes as a control. Thus, the BEGYN study was designed as an observational study, using validated methods to assess physical activity, cardiopulmonary fitness, body composition, psychological parameters, and extensive blood tests (e.g., immune status, vitamin D and selenium) during the first year of antineoplastic therapy after diagnosis of non-metastatic breast cancer. To gain information even after a longer period the BEGYN study is designed to collect data over one year after diagnosis. This study will shed light into the dynamics of physiological and psychological variables and the course of the disease during the first year after initiation of antineoplastic therapy in breast cancer patients in correlation with the physical activity. Ultimately, this study will lay the basis to develop individualized recommendations for exercise in breast cancer patients to improve the quality of life and prognosis.

# 2 MATERIALS AND METHODS

## 2.1 Study Population

The BEGYN study will assess 110 female patients with non-metastatic invasive breast cancer prior to the initiation of antineoplastic therapy. The patients will be followed for one year after diagnosis. Since the study focuses on variables that are heavily influenced by gender (e.g., physical fitness and body composition), we did not include male breast cancer patients. Inclusion and exclusion criteria ensure that patients can undergo spiroergometry, blood tests, assessment of physical activities and psychological parameters during the first year after the diagnosis of breast cancer. The detailed inclusion criteria and exclusion criteria are given in **Table 1**.

## 2.2 Study Schedule

The patients are enrolled to the BEGYN study after initial diagnosis. The baseline study visit is scheduled before the initiation of any antineoplastic therapy, followed by quarterly follow up visits. During each visit, patients undergo a clinical assessment, spiroergometry on a treadmill, blood tests, measurement of the body composition by bioimpedance analysis, plicometry, validated psychological questionnaires and other assessments (**Figure 1**).

## 2.3 Clinical Assessment

Routine assessment during quarterly follow-up visits includes an anamnesis focused on potential side effects of antineoplastic therapies, measuring the body weight and blood pressure.

## 2.4 Assessment of Physical Activity and Exercise

### 2.4.1 Patient Self-Assessment Diary

Each patient will be asked to document her daily sporting activities in a standardized self-assessment study diary. The patients will be instructed by study personnel how to use the diary during recruitment and during each follow-up visit. The study personnel check the completeness and accuracy of the diary and discuss potential improvements with the patients on each follow-up visit. The diary will be used to document the following points:

- Medically relevant information (change of medication or nutritional supplements, fever, symptoms etc.)
- Daily sportive activities
- Weekly read outs of the fitness tracker
- Weekly psychological questionnaires
- Questions and notes that the study participants might have.

As a standardized measure of physical activity the metabolic equivalent task (MET) will be used to describe the metabolic turnover of the patients even when performing different sportive activities (46, 47).

**TABLE 1** | Inclusion criteria and exclusion criteria of the BEGYN study.

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Female sex<br>• Age ≥ 18 years<br>• Invasive, non-metastatic breast cancer<br>• Sufficient language skills to fill the questionnaires and to write an activity diary<br>• Sufficient technical skills or support for using a smart phone and fitness tracker<br>• Given written informed consent | • Any antineoplastic treatment or invasive procedures (e.g., surgery for venous port) prior to baseline measurement<br>• Life expectancy < 12 months<br>• Non-invasive disease (e.g., carcinoma *in situ*)<br>• Previous or current history of other neoplasia<br>• Inability to perform a spiroergometry on a tread mill<br>• Pregnant or nursing women |

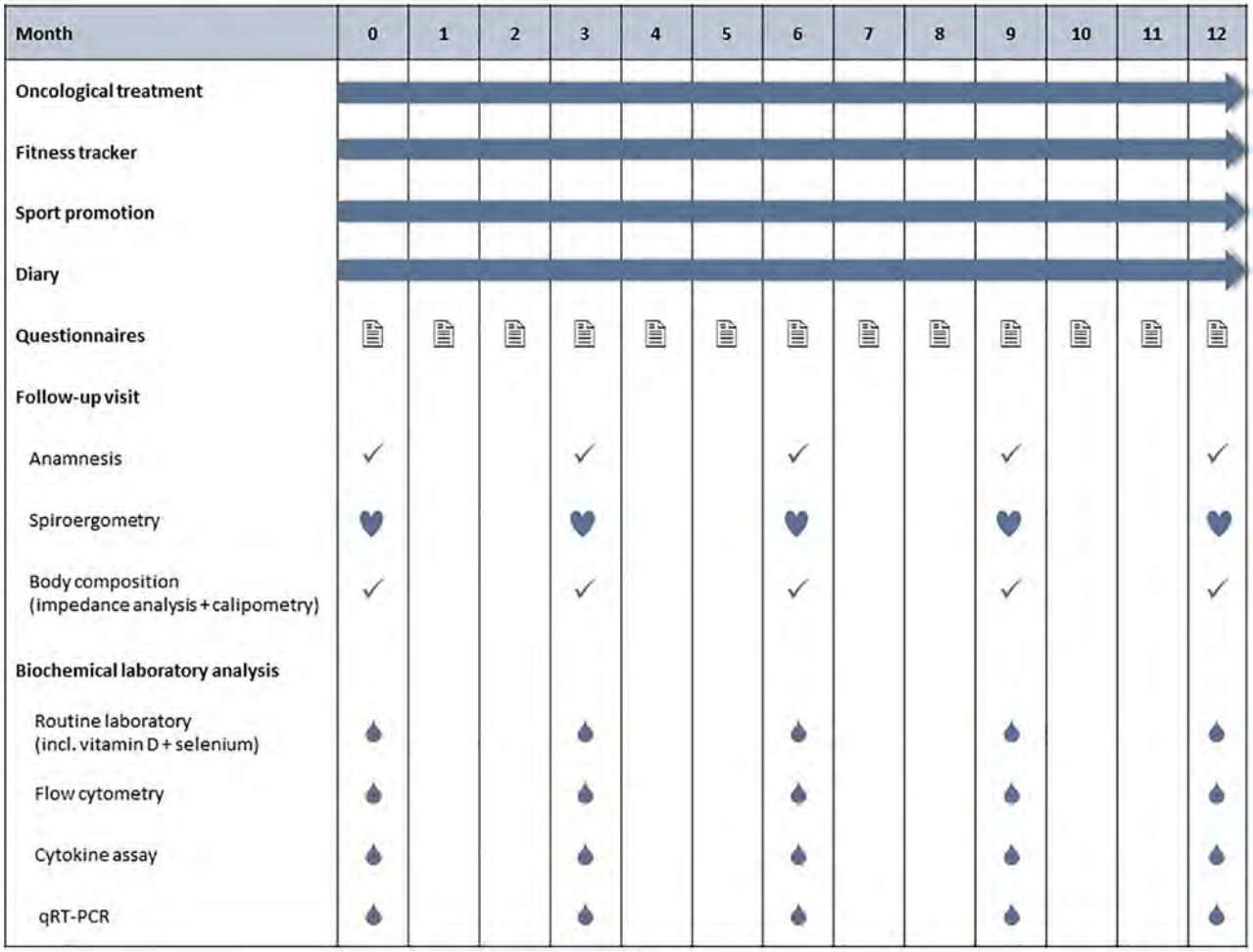



**FIGURE 1** | Schedule for the BEGYN study. All patients are asked to write down their physical activities in a diary (type and duration of exercise) and to continuously wear a fitness tracker. Study visits are scheduled quarterly, with the first visit taking place before initiation of antineoplastic therapy.

### 2.4.2 Spiroergometry

During each of the five study visits the patients perform a spiroergometry on a treadmill (XRCISE RUNNER MED™ by Cardiowise, ERGO-FIT™, Pirmasens, Germany) for the assessment of cardiopulmonary fitness (48). After a technical introduction for the patient, the calibration of the aeroman™ and a baseline spirometry in seated position, the patients start walking at an individually determined speed, typically 4 kmph. Subsequently, the patient is challenged according to a standardized, validated protocol that ensures a linear increase in Oxygen uptake response (49). For inter- and intraindividual comparison, the time course of work rate in watts ($WR_{(t)}$) is calculated using the formula published by Porszasz et al. (49) $WT(t) = m * g * \nu(t) * \sin(\alpha)$, where m is body mass in kg, g is the gravitational acceleration (9.81 $m*s^{-2}$), $\nu(t)$ is the time course of velocity in meters per second, and $\alpha$ is the angle of inclination. The speed or gradient of the treadmill is increased by 0.5 kmph or 1 percent every 2 minutes to intensify the level of exertion. After each interval, the patient breathes through a tightly fitting spirometer mouthpiece (aeroman™ professional, ACEOS GmbH, Fürth, Germany) according to a validated protocol (50). The measurement will be terminated once the patient reaches a maximum heart rate defined as 220 – age (bpm) or a respiratory quotient >1. Furthermore, the subjective perception of exertion according to Borg >17 (51), dizziness, dyspnea, nausea or pain will lead to termination of the spiroergometry (52). The patient can interrupt the measurement due to subjective exhaustion at any time. This will reveal intraindividual longitudinal changes during the first year after the diagnosis of breast cancer. The ventilatory threshold (VT) will be used as a submaximal indicator of general cardiopulmonary fitness (53). VT represents the excessive increase of carbon dioxide output compared to oxygen uptake. In addition, heart rate (HR), oxygen uptake ($VO_2$), carbon dioxide release ($VCO_2$), respiratory quotient (RQ), breathing frequency (BF) and respiratory minute volume (VE) will be assessed to allow the analysis of endurance performance. The measurements obtained with the spiroergometry are given in **Table 2**.

**TABLE 2** | Spiroergometry.

| Description | Abbreviation | Unit |
|---|---|---|
| Heart rate | HR | Beats per minute |
| Oxygen uptake | $VO_2$ | L/min |
| Carbon dioxide release (l/min) | $VCO_2$ | L/min |
| Respiratory quotient | RQ | $VO_2/VCO_2$ |
| Breathing frequency | BF | Breaths per minute |
| Respiratory minute volume | VE | L/min |

### 2.4.3. Fitness Tracker

Physical activity is assessed daily by supplying each patient uses a commercial fitness tracker (Fitbit charge 3™ (Fitbit Inc., San Francisco) that will be linked to her smartphone (54). Study personnel assists the patients and – if required – their associate to install the smartphone app and to setup the measurements. The patients are requested to transcribe the measurements of their fitness tracker into their study diary weekly. Those values are shown in **Table 3**.

## 2.5 Body Composition

### 2.5.1. Bioelectrical Impedance Analysis

The body composition will be determined based on bioelectrical impedance analysis (BIA) (TANITA scale™, Tanita Europe BV, Stuttgart). The test person stands barefoot on a body scale and holds sensors in both hands. Using the impedance between the four measuring points, numerous data can be collected that provide information on the muscle, fat, bone and water content of the whole body and individual compartments. Bioimpedance analysis is routinely used in the context of nutritional advice and sports medicine, but it can also shed light into disease processes, such as hemodialysis patients (55) (**Table 4**). When accessible, the body composition will also be estimated by using routine CT scans of the study patients as previously published (56).

### 2.5.2 Plicometry (Calipometry)

Plicometry allows a standardized estimate of the body fat status which can change under influences such as sport, chemotherapy or cancer (57–60). In the BEGYN study, fat distribution is assessed using the skinfold measurement using the 3 point-method (triceps, suprailiac skinfold, and thigh) according to Jackson and Pollock (61). (**Figure 2**). The total body subcutaneous fat tissue (in kg) was estimated from the plicometry measurements using the formula (61):

**TABLE 3** | Measurements with the fitness tracker.

| Description | Abbreviation | Registration interval | Unit |
|---|---|---|---|
| **Core stats** | | **Daily** | |
| Steps taken | | Daily | Count |
| Resting heart rate | RHR | Daily | Beats per minute |
| Calories burned | Cal | Daily | Kcal |
| **Workout stats** | | **Real-time** | |
| Elapsed time | | Real-time | Minute |
| Distance covered | | Real-time | Km |
| Calories burned | | Real-time | Kcal |
| Average heart rate | øHR | Real-time | Beats per minute |
| Maximum heart rate | HRmax | Real-time | Beats per minute |

**TABLE 4** | Measurements by scale and bioimpedance analysis.

| Item | Unit |
|---|---|
| Weight | kg |
| Total body fat | % |
| Total muscle mass | kg |
| Bone mass | kg |
| Body-Mass-Index | $Kg/m^2$ |
| Basal metabolic rate | kcal |
| Metabolic age | years |
| Total body water | % |
| Visceral fat | kg |
| Segmental muscle mass in arms, legs, and torso | kg |
| Segmental body fat in arms, legs, and torso | % |

$$\text{Total body subcutaneous fat (kg)} = [(4.95/(1.0994921 - (0.0009929^{*}S) + (0.0000023^{*}S^{2}) - (0.0001392^{*}\text{age\{in years\}}))) - 4.5]^{*}100.$$

S is the sum of the skinfold thicknesses measured at the triceps, the suprailiac skinfold and the thigh.

## 2.6 Nutritional Habits, Intake Of Food Supplements, Self-Medications, and Lifestyle

According to the guideline, a Mediterranean diet was recommended to all patients (39). Nutritional habits were assessed using a questionnaire with a focus on characteristic dietary patterns. In addition, sleeping, smoking, and drinking habits, the use of food supplements and self-medication as well as exposure to sunlight and use of sun protection were assessed using questionnaires and the self-assessment diary, respectively.

## 2.7 Biomarkers

Cancer, antineoplastic therapy as well as physical activity are closely related with biomarkers (22, 62–66).

### 2.7.1 Blood Count, Biochemical Laboratory Markers

For disease monitoring and adjustment of the antineoplastic therapy, multiple biomarkers are routinely assessed during the quarterly study visits (**Table 5**). In addition, the BEGYN study will include vitamin D and selenium concentrations since they are often discussed as potentially relevant to cancer biology (69–72).

### 2.7.2 Leukocyte Subsets

Peripheral blood mononuclear cells (PBMCs) will be obtained from 9,6 ml anticoagulated blood samples by Ficoll density gradient centrifugation and resuspended in 90% fetal calf serum + 10% dimethylsulphoxide. Plasma supernatant will be collected and all biosamples will be cryopreserved at -80°C until further processing (73).

The underlying disease, the antineoplastic therapies and physical activity can have a profound impact on the immune system, respectively (26, 74–77). The number of 36 circulating leukocyte subsets will be assessed by flow cytometry using a panel of validated antibody stainings (**Table 6**), based on previous

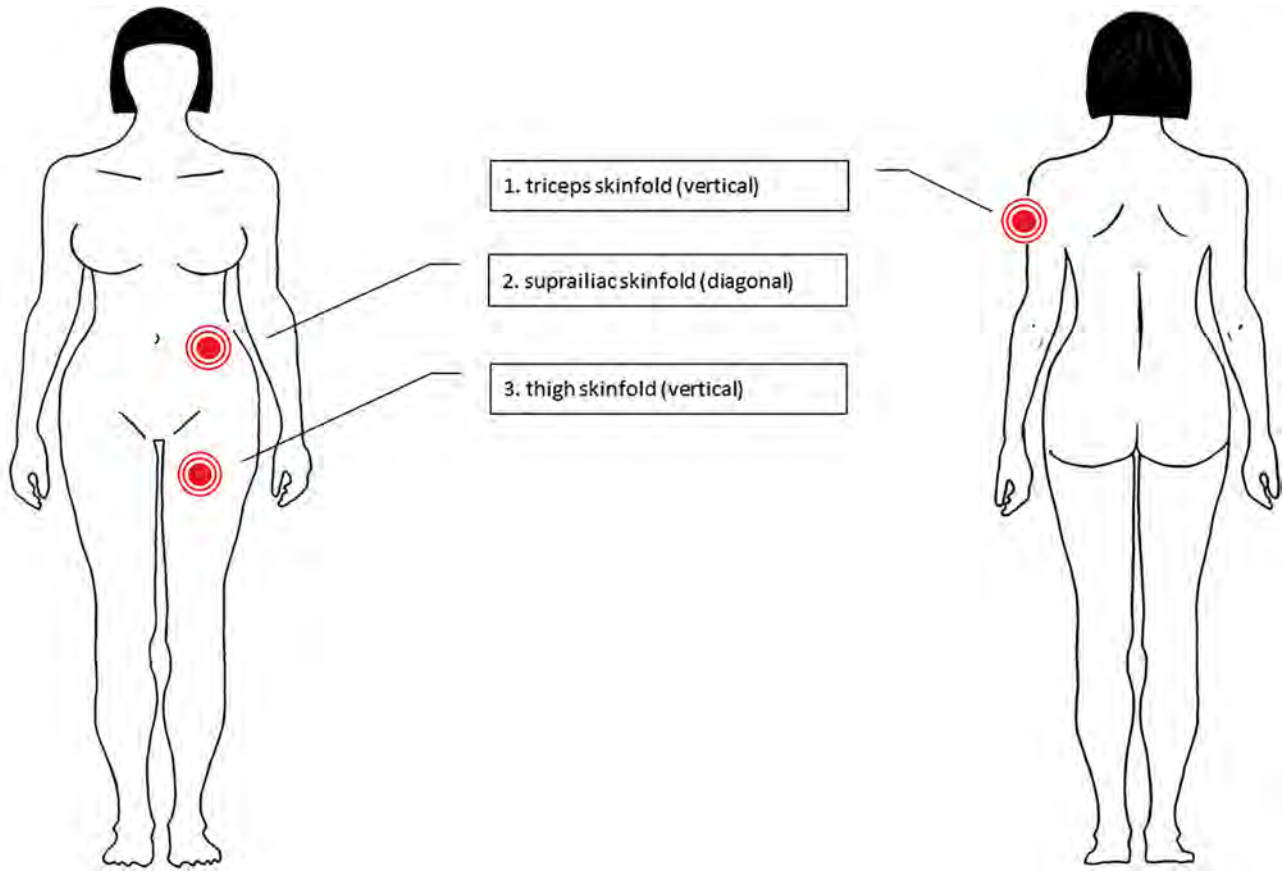



**FIGURE 2** | Plicometry sites of measurement (58, 59). Skinfold measurement using the 3 point-method (1 = triceps, 2 = suprailiac skinfold; 3 = thigh).

studies (73, 78). Cells will be analyzed with FACSCelesta™ (BD Biosciences, Franklin Lakes, New Jersey, USA) (79).

### 2.7.3 Cytokine Profiles

Plasma cytokine profiles will be measured by Luminex® xMAP™ technology (Austin Texas, USA) since they reflect the activity of various immune cells (**Table 7**). Luminex® xMAP™ technology performed on MAGPIX™ instruments, enables the simultaneous quantification of up to 50 target proteins or nucleic acids (80) and have been validated for numerous immunological studies, including breast cancer (20, 62, 81) and infections (82). Superparamagnetic microsphere beads are conjugated with a distinct monoclonal antibody. The beads themselves are dyed with varying amounts of red and infrared fluorophores to allow clear assignment to a specific bead region. MAGPIX™ fluorescence imager-based instruments use a LED illumination/CCD camera detection system for both bead region identification and reporter fluorophore-based analyte quantification (83).

### 2.7.4 Gene Expression Profiles

The expression of selected mRNA transcripts related to breast cancer and inflammation will be measured by a quantitative real-time PCR (qPCR). The method used is based on a previously published technique (73). Total RNA will be isolated from PMBCs using the High Pure RNA Isolation Kit (Roche, Basel, Suisse). Reverse transcription will be performed using SuperScript™ VILO IV cDNA Synthesis Kit (Invitrogen, Thermo Fisher Scientific) followed by the cDNA purification using QIAquick™ PCR Purification Kit (Qiagen, Hilden). Concentration and purity determination of the isolated RNA will be performed with NanoDrop™ (Thermo Fisher Scientific, Waltham, Massachusetts, USA). TaqMan™ Gene Expression Assays (Applied Biosystems, Thermo Fisher Scientific, Waltham, Massachusetts, USA) will be used to perform qRT-PCR of immunological key transcription factors TBX21, RORC, GATA3, FOXP3 (84–88). The Δct-values will be calculated using ACTB, EEF1A1, and 18S as a standard. Values will be normalized to the data from the samples taken at the baseline visit.

## 2.8 Assessment of Psychological Parameters

The assessment of psychological parameters will be performed by using standardized questionnaires that were validated for (breast) cancer patients, respectively (89–98). A list of questionnaires is shown in **Table 8**. Moreover, the patients have the opportunity to report individual thoughts as free texts and during the study visits.

**TABLE 5 |** Laboratory values, intervals of assessment and reference values.

| Parameter | Assessment interval | Vial | Unit | reference value |
|---|---|---|---|---|
| **Blood count** | | | | |
| Erythrocytes | quarterly | EDTA | 10\S\12/l | 4.00 – 5.20 |
| Hb | quarterly | EDTA | g/dl | 12.0 – 16.0 |
| Leukocytes | quarterly | EDTA | 10\S\9/l | 3.9 – 10.2 |
| Thrombocytes | quarterly | EDTA | 10\S\9/l | 140 – 400 |
| **Differential leukocyte count** | | | | |
| Neutrophils rel. | quarterly | EDTA | % | 42.0 – 77.0 |
| Neutrophils abs. | quarterly | EDTA | 10\S\9/l | 1.5 – 7.7 |
| Lymphocytes | quarterly | EDTA | % | 25.0 – 45.0 |
| Monocytes | quarterly | EDTA | % | 2.0 – 10.0 |
| Eosinophils | quarterly | EDTA | % | 0.0 – 5.0 |
| Basophils | quarterly | EDTA | % | 0.0 – 1.0 |
| **Biochemical parameters** | | | | |
| Sodium | quarterly | Li-Heparin-Plasma | mmol/l | 135 – 145 |
| Potassium | quarterly | Li-Heparin-Plasma | mmol/l | 3.5 – 5.1 |
| Calcium | quarterly | Li-Heparin-Plasma | mmol/l | 2.2 – 2.6 |
| Magnesium | quarterly | Li-Heparin-Plasma | mmol/l | 0.66 – 1.07 |
| Iron | quarterly | Li-Heparin-Plasma | µg/dl | 33 – 193 |
| Creatinin | quarterly | Li-Heparin-Plasma | mg/dl | 0.50 – 0.90 |
| Urea | quarterly | Li-Heparin-Plasma | mg/dl | 17 – 48 |
| Uric acid | quarterly | Li-Heparin-Plasma | mg/dl | 2.5 – 5.7 |
| Glucose | quarterly | Li-Heparin-Plasma | mg/dl | 60 – 100 |
| Protein | quarterly | Serum | g/l | 66 – 87 |
| Albumin | quarterly | Serum | g/l | 35 – 52 |
| Cholesterol | quarterly | Li-Heparin-Plasma | mg/dl | <200 |
| Triglycerides | quarterly | Li-Heparin-Plasma | mg/dl | <150 |
| CK | quarterly | Li-Heparin-Plasma | U/l | 0 – 170 |
| ASAT | quarterly | Li-Heparin-Plasma | U/l | 0 – 35 |
| ALAT | quarterly | Li-Heparin-Plasma | U/l | 0 – 35 |
| gamma-GT | quarterly | Li-Heparin-Plasma | U/l | <40 |
| Alkaline phosphatase | quarterly | Li-Heparin-Plasma | U/l | 35 – 104 |
| Bilirubin | quarterly | Li-Heparin-Plasma | mg/dl | <1.2 |
| Lipase | quarterly | Li-Heparin-Plasma | U/l | 13 – 60 |
| LDH | quarterly | Li-Heparin-Plasma | U/l | 0 – 262 |
| CRP | quarterly | Li-Heparin-Plasma | mg/l | 0.0 – 5.0 |
| HbA1c | quarterly | EDTA | % | <6.0 |
| LDL-Cholesterol | quarterly | Li-Heparin-Plasma | mg/dl | <130 |
| HDL-Cholesterol | quarterly | Li-Heparin-Plasma | mg/dl | 45 – 65 |
| VLDL-Cholesterol | quarterly | Li-Heparin-Plasma | mg/dl | <35 |
| Interleukin-6 | quarterly | Li-Heparin-Plasma | pg/ml | <7 |
| Selenium | quarterly | Serum | µg/l | 50 – 120 (67) |
| Vitamin D-25-OH | quarterly | Serum | ng/ml | 30 – 100 (68) |
| **Hormones** | | | | |
| TSH | quarterly | Li-Heparin-Plasma | µIU/ml | 0.27 – 4,2 |
| fT3 | quarterly | Li-Heparin-Plasma | pg/ml | 2.0 – 4.4 |
| fT4 | quarterly | Li-Heparin-Plasma | ng/dl | 0.93 – 1.7 |
| Cortisol | quarterly | Serum | µg/dl | 4.82 – 19.5* |
| Insulin | quarterly | Serum | µIU/ml | <29.1 |
| ß-hCG | quarterly | Serum | mIU/ml | <1.0 |
| **Tumor marker** | | | | |
| CA 15-3 | optional | Serum | U/ml | <26.2 |

**Reference values for Cortisol vary depending on the time of blood collection. As in the BEGYN study, samples were routinely taken in the morning these standard values were used.*

### 2.8.1 Quality of Life

The overall quality of life is assessed using the Quality of Life Questionnaire (QLQ-C30 version 3.0) which has been developed and validated by the European Organisation for Research and Treatment of Cancer (EORTC) to explore quality of life among cancer patients (90). The supplementary questionnaire QLQ-BR23 will be used to record symptoms specific for breast cancer (95). In sum, a score from 0 – 100 can be calculated allowing the quantification of the impairments regarding the patient's health and quality of life.

### 2.8.2 Mental Health

The questionnaire "Mental health scales" (MHS) (92) was used to assess the psychological integrity of the study participants, in order to evaluate the development of the patients' personality throughout the study duration. The questionnaire consists out of seven scales (autonomy (17 items), willpower (14 items), acceptance of live (8 items), self-reflection (12 items), finding of a meaning (7 items), naturalness (10 items) and social integration (8 items)), which yields a total of 76 items. The

**TABLE 6 |** Leukocyte subsets.

| population | Surface antigens |
|---|---|
| **B cells** | |
| innate B cells | CD19+ CD27- IgD- IgM- |
| naïve B cells | CD19+ CD27- IgD+ IgM+ |
| memory B cells | CD19+ CD27+ |
| marginal zone memory B cells | CD19+ CD27+ IgD+ IgM+ |
| IgM memory B cells | CD19+ CD27+ IgD- IgM+ |
| class switched memory B cells | CD19+ CD27+ IgD- IgM- |
| late memory B cells | CD19+ CD27+ CD38+ IgM+ |
| plasmablasts | CD19+ CD27+ $CD38^{bright}$ IgM- |
| transitonal B cells | CD19+ CD20+ CD27- CD38+ |
| pre-naïve B cells (B1 cells) | CD20+ CD27+ CD43+ CD70- |
| B2 cells | CD20+ CD27+ CD43- |
| **T cells** | |
| Th cells with αβ-TCR | TCRαβ+ CD4+ |
| cytotoxic Th cells with αβ-TCR | TCRαβ+ CD8+ |
| memory effector Th cells | CD3+ CD4+ CD62L- CD45RO+ |
| memory central Th cells | CD3+ CD4+ CD62L+ CD45RO+ |
| naïve effector Th cells | CD3+ CD4+ CD62L- CD45RO- |
| naive central Th cells | CD3+ CD4+ CD62L+ CD45RO- |
| memory effector cytotoxic T cells | CD3+ CD8+ CD62L- CD45RO+ |
| memory central cytotoxic T cells | CD3+ CD8+ CD62L+CD45RO+ |
| naïve effector cytotoxic T cells | CD3+ CD8+ CD62L- CD45RO- |
| naïve central cytotoxic T cells | CD3+ CD8+ CD62L+ CD45RO- |
| T cells with γδ-TCR | TCR γδ+ CD3+ CD5+ |
| naïve thymus negative Th cells | CD3+ CD4+ CD31- CD45RO- |
| naïve thymus negative Th cells | CD3+ CD4+ CD31+ CD45RO- |
| Th1 cells | CD3+ CD4+ CD183+ CCR6+ |
| Th2 cells | CD3+ CD4+ CCR4+ CRTH2+ |
| naïve Th1 cells | CD3+ CD4+ CD183+ CD45RO- |
| memory Th1 cells | CD3+ CD4+ CD183+ CD45RO+ |
| naïve Th2 cells | CD3+ CD4+ CD45RO- CRTH2+ |
| memory Th2 cells | CD3+ CD4+ CD45RO+ CRTH2+ |
| regulatory T cells | CD3+ CD4+ CD25+ CD127- |
| **NK cells** | |
| natural killer cells | Lin- CD335+ CD56+ CD16+ |
| memory-like natural killer cells | Lin- CD335+ $CD56^{dim}$ CD16+ |
| intermediate natural killer cells | Lin- CD335+ $CD56^{bright}$ CD16- |
| innate natural killer cells | Lin- CD335+ CD56- CD16- |

**TABLE 7 |** Cytokine profiles measures by Luminex™ (MAGPIX®).

| Cytokine | abbreviation |
|---|---|
| Tumor necrosis factor α | TNFα |
| Interferon γ | IFNγ |
| Interleukin 1α | IL-1α |
| Interleukin 1β | IL-1β |
| Interleukin 2 | IL-2 |
| Interleukin 4 | IL-4 |
| Interleukin 6 | IL-6 |
| Interleukin 10 | IL-10 |
| Interferon γ -induced protein 10 | IP10 |
| Monocyte chemoattractant protein 1 | MCP-1 |
| Granulocyte-macrophage colony-stimulating factor | GM-CSF |

questionnaire is answered with the help of a five-point Likert-scale (*1 = I fully agree*; *5 = I fully disagree*) and an example item is "Generally I am confident".

### 2.8.3 Chronic Fatigue Syndrome

Symptoms of chronic fatigue syndrome (CFS) (93) that affects more than 50% of breast cancer patients and the extent of psychological stress will be assessed using the Distress Thermometer (DT) (96).

### 2.8.4 Anxiety and Depression

The self reported anxiety and distress will be assessed using the HADS (Hospital Anxiety and Depression Scale) questionnaire (89, 97) and the German adaptation of the Distress Thermometer (DT) (94, 96–98).

### 2.8.5 Well-Being

To get an overview of the mental state of the patients, the German questionnaire "Multidimensional Well-being Questionnaire" (MDBQ) (91) has been used in its short version with twelve items (short version A). This questionnaire captures three bipolar dimensions of the current mental state (good mood – bad mood, alertness – fatigue, tranquility – inquietude) of the breast cancer patients. The questionnaire presents twelve adjectives (e.g., satisfied, flabby, good etc.) and with the help of a five-point Likert-scale (*1 = not at all*; *5 = very much*) the patients rate their instant feeling. Cronbachs'α is between 0.86 and 0.94, indicating a good consistency of the scale.

## 2.9 Sample Size Calculation and Statistical Analyses

The Institute for Medical Biometry, Epidemiology and Medical Informatics (IMBEI) Saarland University is supporting the sample size calculation, study design, data management and evaluation using PASS 2019 (NCSS, LLC, Kaysville, Utah, USA) and SPSS (Version 27 IBM SPSS Statistics, Armonk, New York, USA). Data were collected by using Excel 2019 (Microsoft, Redmond, USA). A sample size of 110 produces a two-sided 95% confidence interval with a distance from the mean to the limits that is equal to 2.835 when the estimated standard deviation is 15.0. A sample size of 110 produces a two-sided 95% confidence interval with a width equal to 0.187 when the sample proportion is 0.50.

Continuous measures are presented as means ± standard deviations (SD) or medians (range). Categorical variables are presented as frequencies (percentage). For continuous variables normality is tested using Shapiro-Wilk-Test. In case of non-rejection of normality two-group comparisons are due to the t-test for two independent samples. For more than two groups, comparisons are due to one-way Analysis of Variance (ANOVA). Comparing two repeated measurements, t-test for 2 dependent samples is used and for more than two we use repeated measures ANOVA. In case of rejection of normality, Mann-Whitney U-test, Kruskal-Wallis-test, Wilcoxon test for two dependent samples and Friedman-test are used, respectively. For group comparisons considering categorical variables the chi-squared test and for repeated measures McNemars's test are applied. Considering possible confounding we use subgroup analyses for categorical subgroups or propensity-score-matching otherwise. Statistical significance will be calculated using appropriate statistical methods with two-sided p-values < 0.05. The statistical analyses are explorative, so there will be no correction for multiple testing.

**TABLE 8 |** Assessment of the psychological parameters (used questionnaires).

| Abbreviation | Name | Nmber of items | Content | Reference |
|---|---|---|---|---|
| **EORTC QLQ-C30** | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 | 30 items | health-related quality of life (QoL) | (95) |
| **EORTC QLQ-BR23** | European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-BReast cancer module 23 | 23 items | health-related quality of life (QoL) in breast cancer patients: systemic therapy side-effects, arm symptoms, breast symptoms, body image and sexual functioning | (95) |
| **MHS** | Mental Health Scales | 76 items | willpower, acceptance of life, self-reflection, finding of a meaning, naturalness and social integration | (92) |
| **HADS** | Hospital Anxiety and Depression Scale | 14 items | level of anxiety and level of depression | (89) |
| **DT** | Distress Thermometer | DT: 1 item Problem list: 39 items | Psychosocial distress and possibly associated problems (practical, family, emotional, spiritual/religious and physical) | (94) |
| **MDWQ** | MultiDimensional Well-being Questionnaire | 12 items | mood, level of alertness and level of calmness | (91) |

Data cleanup will include tests for missing data and plausibility. Depending on the degree of incompleteness or lack of accuracy, all, or some of the data from a patient will be excluded from further evaluation. In the case of a study drop out prior the last follow up visit, the patient's data will only be included, and tests will be performed to identify potential predictors for a study drop-out (e.g., age or weight) that might introduce a bias. The risk of bias will be discussed in any publications of the data.

# 3 DISCUSSION

The BEGYN study will provide a holistic insight into the physical activity in relation to the physiological and psychological dynamics during the first year after diagnosis of non-metastatic breast cancer. The complex interplay between the underlying disease, antineoplastic therapy and individual constitution affects the patient *in toto*. Thus, therapeutic approaches must not be limited to surgery, antineoplastic medication, radiotherapy and psychological intervention alone, but should include the motivation for supportive activities such as exercise, which has great effect on the quality of life and prognosis (35, 99–101). A better knowledge of biomarkers is a prerequisite to assess the effects of complementary therapies and to develop personalized strategies for rehabilitation, e.g., regarding the type and dose of exercise (9). Therefore, the BEGYN study unites multiple validated assessments, allowing cross-linking analyses between the level of physical activity, cardiopulmonary fitness, body composition, biochemical measurements, an in-depth immune status including quantification of circulating lymphocyte subpopulations, mRNA expression and cytokine profiles and an extensive evaluation of psychological factors.

## 3.1 Novelty of the Approach

Whereas most studies investigating the influence of physical activity in breast cancer patients focus on specific activities for three months or less, the BEGYN study will quantify the daily physical activity and cardiorespiratory fitness of breast cancer patients based on objective measurements in the context of the oncological therapy for 12 months after diagnosis. Multiple studies have shown that physical activity can have positive effects in breast cancer patients (4–6, 33–35, 37). Guidelines recommend physical activity during breast cancer treatment, in example in the United States (102), in Great Britain (103), in Germany (39) and others. In particular, physical activity appears to have a positive effect on breast cancer associated fatigue syndrome (3) and on the overall quality of life (104). However, multiple aspects including the underlying mechanisms remain poorly understood. The BEGYN study will contribute important data to understand the influence of physical activity on the dynamics during the first year of breast cancer treatment and may reveal potential modifiers of the patient's well-being.

### 3.1.1 Holistic Approach

To our knowledge, the BEGYN study is one of the largest studies with a very broad approach in breast cancer patients that will allow to identify associations between physical, psychological and laboratory variables, thus linking aspects that are often studied separately in breast cancer patients. Regarding the assessment of physical activity, it will be of particular interest to discuss the results of the BEGYN study in the light of other ongoing highly innovative studies such as the PROTECT study which also includes patients with colorectal cancer and lung cancer (6). One of the major strengths is the continuous recording of the patient's physical activity and well-being by diary and by use of a fitness tracker since physical activity encompasses not only explicit sports activities, which may last a few hours per week, but also activity during everyday activities. Various forms of physical activity have been proposed, such as yoga, Tai Chi Chuan, Nordic walking, jogging, weight training, cycling, dancing and many others (20, 36, 37, 47). However, it has been claimed that individualized recommendations are needed to meet the needs of the patient (6, 105). By using the concept of metabolic equivalents (MET), the BEGYN study will allow comparing effects of physical activities of similar intensities independent of the type of exercise. Since nutrition, food supplements and lifestyle may significantly influence the effects of exercise and antineoplastic therapies, these variables are assessed by using questionnaires and the self-assessment diary.

### 3.1.2 One Year Study Schedule

The BEGYN study will yield an overview on a relatively long period of 12 months after diagnosis, starting before any specific antineoplastic therapy. Thus, the patient will typically be observed beyond the initial steps of therapy, which are also often associated with psychoemotional distress. This may give insight into predictors of a more favorable long-term management towards a new physical and psychological balance. Moreover, the 12 months study period will reduce potential artifacts due to seasonal effects which can, in example, influence outdoor activities and Vitamin D concentrations. The role of Vitamin D in carcinogenesis and cancer therapy is still under debate. Importantly, serial measurements of 2,5 OH Vitamin D concentrations in peripheral blood and assessment of therapeutic Vitamin D intake may give insight into the role of Vitamin D metabolism and may also provide data on the interaction between antineoplastic therapy and Vitamin D. In addition, the BEGYN study will yield serial selenium concentrations and insight on the consumption of selenium by the patients, which often is provided as a self-medication, causing significant financial burden for some patients.

### 3.1.3 Comparison of Different Antineoplastic Therapies

The BEGYN study will allow to compare patients with various antineoplastic therapies, i.e., endocrine therapy, chemotherapy, surgery, and radiotherapy. Due to the strict adherence to the national guideline, therapy concepts are to be expected representative for the German national standard.

### 3.1.4 Immunophenotyping

The BEGYN study will yield a deep insight into the innate and adaptive immune system during the first year after diagnosis of non-metastatic breast cancer (62). Inflammatory processes are a crucial part of the physiological response to cancer cells. Simultaneously, the BEGYN study will shed light on the effects of endocrine therapy and of chemotherapy on the immune system. Moreover, it is well recognized that moderate physical activity is associated with an improved immune status whereas excessive physical activity leads to an increase susceptibility towards (viral) infections (22). Interestingly, natural killer (NK) cells play a key role in sports physiology and in restricting tumor growth (64). Thus, the BEGYN study will be among the first studies to quantify four distinct subsets of NK cells in relation not only to breast cancer and antineoplastic therapy, but also in relation to the extent and type of physical activity.

The BEGYN study also has some limitations, such as the single center approach. However, the data will serve as a basis for designing future multicenter studies. In example, the results of the BEGYN study might help focusing the highly detailed immunophenotyping regarding the characterization of leukocyte subsets, mRNA transcripts and cytokines to the most promising variables in future study protocols. One further limitation of the study is that the quality of self-assessments may underlie intra-individual and inter-individual variations when filling out the self-assessment diary (e.g. daily documentation of physical activities, weekly read outs of the measurements of the fitness tracker etc.). Due to the need of serial measurements of the body composition, ethical concerns on X-ray exposure were the reason to use bioimpedance analysis and plicometry rather than Dual-energy X-ray absorptiometry, which is regarded as the gold standard (106). With regard to the known limitations of bioimpedance analysis and plicometry, we will compare the intra-individual relative changes over time instead of absolute values (107). In addition, we will further extend the data by estimating the body composition from the routine CT scans of the study patients (56). The BEGYN study is an observational study, thus potential causal relationships must be interpreted carefully. Ethical concerns would not allow randomizing patients into a group that would not be encouraged to exercise since this would conflict with the high evidence guidelines. However, the BEGYN study might help defining valid methods of continuous registration of physical activity for future studies to compare the role of various types of exercise, e.g., training of strength versus endurance.

## 3.2 Conclusion

The holistic approach over 12 months including physiological, psychological, and immunological data is the main strength of the BEGYN study. By including a homogeneous group of 110 female non-metastatic breast cancer patients, the study will provide highly valid data on the complex interplay between physical activity, underlying disease, type of therapy and psychological parameters.

The BEGYN study provides a uniquely thorough analysis of non-metastatic breast cancer patient during the first year after diagnosis.

## 3.3 Ethics and Dissemination

The study is carried out at the Department for Gynecology, Saarland University Medical Center and has been approved by the ethics committee of the Medical Association of Saarland (study # 229/18). Written consent is obtained from the patient in accordance with the Declaration of Helsinki. Any amendment to the protocol will require the formal modification and approval by the same local ethics committee that approved the study prior to implementation and will be described transparently in subsequent reports. This study is registered at German Clinical Trials Register (DRKS) (DRKS00024829). Patient recruitment took place between September 2019 and January 2021 and data collection will continue until March 2022.

# ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethics committee of the Medical Association of Saarland (study # 229/18). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

CZ designed the study and wrote the first draft of the manuscript. GW performed sample size calculations, gave advice for statistical analyses and helped drafting the manuscript. CS, JS, CW, CM, LA, ML, L-SS, LK, and IT performed the clinical experiments, helped with the study design, and helped writing the manuscript. CM helps to raise funding and helped writing the manuscript. EK, RS, and SG-F performed the laboratory experiments and helped writing the manuscript. MZ, GS, and E-FS gave advice for the study design, supervised the study, and helped writing the manuscript. All authors contributed to the article and approved the submitted version.

## FUNDING

This work was supported by *miteinander gegen Krebs e.V.* and by the intramural funds of the Saarland University Medical Center.

## ACKNOWLEDGMENTS

The authors would like to thank Dr. Maria Cacacciola-Ketter, Cross against Cancer – *miteinander gegen Krebs e.V.*, Bernd Neuhardt (Laufschule Saarpfalz, Runners Gym Zweibrücken), Ellen Maurer.

## REFERENCES

1. Baumann F, Bloch W, Jäger E. *Sport Und Körperliche Aktivität in Der Onkologie. 1st ed*. Berlin Heidelberg: Springer-Verlag Berlin Heidelberg (2012).
2. Stene GB, Helbostad JL, Balstad TR, Riphagen II, Kaasa S, Oldervoll LM. Effect of Physical Exercise on Muscle Mass and Strength in Cancer Patients During Treatment–A Systematic Review. *Crit Rev Oncol Hematol* (2013) 88:573–93. doi: 10.1016/j.critrevonc.2013.07.001
3. Furmaniak AC, Menig M, Markes MH. Exercise for Women Receiving Adjuvant Therapy for Breast Cancer. *Cochrane Database Syst Rev* (2016) 9: CD005001. doi: 10.1002/14651858.CD005001.pub3
4. Schmidt T, Jonat W, Wesch D, Oberg H-H, Adam-Klages S, Keller L, et al. Influence of Physical Activity on the Immune System in Breast Cancer Patients During Chemotherapy. *J Cancer Res Clin Oncol* (2018) 144:579–86. doi: 10.1007/s00432-017-2573-5
5. Holmen Olofsson G, Jensen AWP, Idorn M, Thor Straten P. Exercise Oncology and Immuno-Oncology; A (Future) Dynamic Duo. *Int J Mol Sci* (2020) 21:E3816. doi: 10.3390/ijms21113816
6. Mallard J, Hucteau E, Schott R, Petit T, Demarchi M, Belletier C, et al. Evolution of Physical Status From Diagnosis to the End of First-Line Treatment in Breast, Lung, and Colorectal Cancer Patients: The PROTECT-01 Cohort Study Protocol. *Front Oncol* (2020) 10:1304. doi: 10.3389/fonc.2020.01304
7. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2021) 71:209–49. doi: 10.3322/caac.21660
8. Fallowfield L, Osborne S, Langridge C, Monson K, Kilkerr J, Jenkins V. Implications of Subcutaneous or Intravenous Delivery of Trastuzumab; Further Insight From Patient Interviews in the PrefHer Study. *Breast* (2015) 24:166–70. doi: 10.1016/j.breast.2015.01.002
9. Invernizzi M, de Sire A, Venetis K, Cigna E, Carda S, Borg M, et al. Quality of Life Interventions in Breast Cancer Survivors: State of the Art in Targeted Rehabilitation Strategies. *Anticancer Agents Med Chem* (2021). doi: 10.2174/1871520621666210609095602
10. Zaidi S, Hussain S, Verma S, Veqar Z, Khan A, Nazir SU, et al. Efficacy of Complementary Therapies in the Quality of Life of Breast Cancer Survivors. *Front Oncol* (2017) 7:326. doi: 10.3389/fonc.2017.00326
11. Luo X-C, Liu J, Fu J, Yin H-Y, Shen L, Liu M-L, et al. Effect of Tai Chi Chuan in Breast Cancer Patients: A Systematic Review and Meta-Analysis. *Front Oncol* (2020) 10:607. doi: 10.3389/fonc.2020.00607
12. Invernizzi M, de Sire A, Lippi L, Venetis K, Sajjadi E, Gimigliano F, et al. Impact of Rehabilitation on Breast Cancer Related Fatigue: A Pilot Study. *Front Oncol* (2020) 10:556718. doi: 10.3389/fonc.2020.556718
13. Wirtz P, Baumann FT. Physical Activity, Exercise and Breast Cancer - What Is the Evidence for Rehabilitation, Aftercare, and Survival? A Review. *Breast Care (Basel)* (2018) 13:93–101. doi: 10.1159/000488717
14. Bower JE, Bak K, Berger A, Breitbart W, Escalante CP, Ganz PA, et al. Screening, Assessment, and Management of Fatigue in Adult Survivors of Cancer: An American Society of Clinical Oncology Clinical Practice Guideline Adaptation. *J Clin Oncol* (2014) 32:1840–50. doi: 10.1200/JCO.2013.53.4495
15. Invernizzi M, Lopez G, Michelotti A, Venetis K, Sajjadi E, De Mattos-Arruda L, et al. Integrating Biological Advances Into the Clinical Management of Breast Cancer Related Lymphedema. *Front Oncol* (2020) 10:422. doi: 10.3389/fonc.2020.00422
16. Bailey S, Lin J. The Association of Osteoporosis Knowledge and Beliefs With Preventive Behaviors in Postmenopausal Breast Cancer Survivors. *BMC Womens Health* (2021) 21:297. doi: 10.1186/s12905-021-01430-1
17. Uth J, Fristrup B, Haahr RD, Brasso K, Helge JW, Rørth M, et al. Football Training Over 5 Years Is Associated With Preserved Femoral Bone Mineral Density in Men With Prostate Cancer. *Scand J Med Sci Sports* (2018) 28:61–73. doi: 10.1111/sms.13242
18. Dieli-Conwright CM, Parmentier J-H, Sami N, Lee K, Spicer D, Mack WJ, et al. Adipose Tissue Inflammation in Breast Cancer Survivors: Effects of a 16-Week Combined Aerobic and Resistance Exercise Training Intervention. *Breast Cancer Res Treat* (2018) 168:147–57. doi: 10.1007/s10549-017-4576-y
19. Zimmer P, Schmidt ME, Prentzell MT, Berdel B, Wiskemann J, Kellner KH, et al. Resistance Exercise Reduces Kynurenine Pathway Metabolites in Breast Cancer Patients Undergoing Radiotherapy. *Front Oncol* (2019) 9:962. doi: 10.3389/fonc.2019.00962
20. Loo LWM, Nishibun K, Welsh L, Makolo T, Chong CD, Pagano I, et al. Using a Cultural Dance Program to Increase Sustainable Physical Activity for Breast Cancer Survivors-A Pilot Study. *Complement Ther Med* (2019) 47:102197. doi: 10.1016/j.ctim.2019.102197
21. Xu Y, Rogers CJ. Physical Activity and Breast Cancer Prevention: Possible Role of Immune Mediators. *Front Nutr* (2020) 7:557997. doi: 10.3389/fnut.2020.557997
22. Rooney BV, Bigley AB, LaVoy EC, Laughlin M, Pedlar C, Simpson RJ. Lymphocytes and Monocytes Egress Peripheral Blood Within Minutes After Cessation of Steady State Exercise: A Detailed Temporal Analysis of Leukocyte Extravasation. *Physiol Behav* (2018) 194:260–7. doi: 10.1016/j.physbeh.2018.06.008
23. Hinshaw DC, Shevde LA. The Tumor Microenvironment Innately Modulates Cancer Progression. *Cancer Res* (2019) 79:4557–66. doi: 10.1158/0008-5472.CAN-18-3962
24. Ashcraft KA, Warner AB, Jones LW, Dewhirst MW. Exercise as Adjunct Therapy in Cancer. *Semin Radiat Oncol* (2019) 29:16–24. doi: 10.1016/j.semradonc.2018.10.001
25. Cannioto RA, Hutson A, Dighe S, McCann W, McCann SE, Zirpoli GR, et al. Physical Activity Before, During, and After Chemotherapy for High-Risk Breast Cancer: Relationships With Survival. *JNCI: J Natl Cancer Institute* (2021) 113:54–63. doi: 10.1093/jnci/djaa046
26. Schmidt T, van Mackelenbergh M, Wesch D, Mundhenke C. Physical Activity Influences the Immune System of Breast Cancer Patients. *J Cancer Res Ther* (2017) 13:392–8. doi: 10.4103/0973-1482.150356
27. van der Leeden M, Huijsmans RJ, Geleijn E, de Rooij M, Konings IR, Buffart LM, et al. Tailoring Exercise Interventions to Comorbidities and Treatment-Induced Adverse Effects in Patients With Early Stage Breast Cancer Undergoing Chemotherapy: A Framework to Support Clinical Decisions. *Disability Rehabil* (2018) 40:486–96. doi: 10.1080/09638288.2016.1260647

28. Mehnert A, Brähler E, Faller H, Härter M, Keller M, Schulz H, et al. Four-Week Prevalence of Mental Disorders in Patients With Cancer Across Major Tumor Entities. *J Clin Oncol* (2014) 32:3540–6. doi: 10.1200/JCO.2014.56.0086
29. Ribeiro FE, Palma MR, Silva DTC, Tebar WR, Vanderlei LCM, Fregonesi CEPT, et al. Relationship of Anxiety and Depression Symptoms With the Different Domains of Physical Activity in Breast Cancer Survivors. *J Affect Disord* (2020) 273:210–4. doi: 10.1016/j.jad.2020.03.110
30. Alexander S, Minton O, Stone PC. Evaluation of Screening Instruments for Cancer-Related Fatigue Syndrome in Breast Cancer Survivors. *J Clin Oncol* (2009) 27:1197–201. doi: 10.1200/JCO.2008.19.1668
31. Schmidt ME, Wiskemann J, Armbrust P, Schneeweiss A, Ulrich CM, Steindorf K. Effects of Resistance Exercise on Fatigue and Quality of Life in Breast Cancer Patients Undergoing Adjuvant Chemotherapy: A Randomized Controlled Trial. *Int J Cancer* (2015) 137:471–80. doi: 10.1002/ijc.29383
32. Duijts SFA, Faber MM, Oldenburg HSA, van Beurden M, Aaronson NK. Effectiveness of Behavioral Techniques and Physical Exercise on Psychosocial Functioning and Health-Related Quality of Life in Breast Cancer Patients and Survivors–A Meta-Analysis. *Psychooncology* (2011) 20:115–26. doi: 10.1002/pon.1728
33. Lucía A, Earnest C, Pérez M. Cancer-Related Fatigue: Can Exercise Physiology Assist Oncologists? *Lancet Oncol* (2003) 4:616–25. doi: 10.1016/s1470-2045(03)01221-x
34. Barsevick AM, Newhall T, Brown S. Management of Cancer-Related Fatigue. *Clin J Oncol Nurs* (2008) 12:21–5. doi: 10.1188/08.CJON.S2.21-25
35. Cramp F, Byron-Daniel J. Exercise for the Management of Cancer-Related Fatigue in Adults. *Cochrane Database Syst Rev* (2012) 11:CD006145. doi: 10.1002/14651858.CD006145.pub3
36. Schmitz KH, Ahmed RL, Troxel A, Cheville A, Smith R, Lewis-Grant L, et al. Weight Lifting in Women With Breast-Cancer-Related Lymphedema. *N Engl J Med* (2009) 361:664–73. doi: 10.1056/NEJMoa0810118
37. Baumann FT, Reike A, Reimer V, Schumann M, Hallek M, Taaffe DR, et al. Effects of Physical Exercise on Breast Cancer-Related Secondary Lymphedema: A Systematic Review. *Breast Cancer Res Treat* (2018) 170:1–13. doi: 10.1007/s10549-018-4725-y
38. Baumann FT, Reike A, Hallek M, Wiskemann J, Reimer V. Does Exercise Have a Preventive Effect on Secondary Lymphedema in Breast Cancer Patients Following Local Treatment? - A Systematic Review. *Breast Care (Basel)* (2018) 13:380–5. doi: 10.1159/000487428
39. *Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). S3-Leitlinie Früherkennung, Diagnose, Therapie Und Nachsorge Des Mammakarzinoms, Version 4.4* (2021). Available at: http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom (Accessed July 24, 2021). AWMF Registernummer: 032-045OL.
40. Deluche E, Leobon S, Desport JC, Venat-Bouvet L, Usseglio J, Tubiana-Mathieu N. Impact of Body Composition on Outcome in Patients With Early Breast Cancer. *Support Care Cancer* (2018) 26:861–8. doi: 10.1007/s00520-017-3902-6
41. Khalil SF, Mohktar MS, Ibrahim F. The Theory and Fundamentals of Bioimpedance Analysis in Clinical Status Monitoring and Diagnosis of Diseases. *Sensors (Basel)* (2014) 14:10895–928. doi: 10.3390/s140610895
42. Cespedes Feliciano E, Chen WY. Clinical Implications of Low Skeletal Muscle Mass in Early-Stage Breast and Colorectal Cancer. *Proc Nutr Soc* (2018) 77:382–7. doi: 10.1017/S0029665118000423
43. Migueles JH, Cadenas-Sanchez C, Ekelund U, Delisle Nyström C, Mora-Gonzalez J, Löf M, et al. Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes: A Systematic Review and Practical Considerations. *Sports Med* (2017) 47:1821–45. doi: 10.1007/s40279-017-0716-0
44. Skender S, Ose J, Chang-Claude J, Paskow M, Brühmann B, Siegel EM, et al. Accelerometry and Physical Activity Questionnaires - A Systematic Review. *BMC Public Health* (2016) 16:515. doi: 10.1186/s12889-016-3172-0
45. Reimers AK, Knapp G, Reimers C-D. Effects of Exercise on the Resting Heart Rate: A Systematic Review and Meta-Analysis of Interventional Studies. *J Clin Med* (2018) 7:E503. doi: 10.3390/jcm7120503
46. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-Locke C, et al. Compendium of Physical Activities: A Second Update of Codes and MET Values. *Med Sci Sports Exerc* (2011) 43:1575–81. doi: 10.1249/MSS.0b013e31821ece12
47. Baumann FT, Bieck O, Oberste M, Kuhn R, Schmitt J, Wentrock S, et al. Sustainable Impact of an Individualized Exercise Program on Physical Activity Level and Fatigue Syndrome on Breast Cancer Patients in Two German Rehabilitation Centers. *Support Care Cancer* (2017) 25:1047–54. doi: 10.1007/s00520-016-3490-x
48. Saemann L, Lachner K, Wenzel F. Cardiac Frequency and Cutaneous Microcirculation During and After Exercising in the View of Physical Condition. *Clin Hemorheol Microcirc* (2017) 67:221–7. doi: 10.3233/CH-179203
49. Porszasz J, Casaburi R, Somfay A, Woodhouse LJ, Whipp BJ. A Treadmill Ramp Protocol Using Simultaneous Changes in Speed and Grade. *Med Sci Sports Exerc* (2003) 35:1596–603. doi: 10.1249/01.MSS.0000084593.56786.DA
50. Gerhardt O. *Evaluation Unterschiedlicher Spirometriesysteme (3) Für Den Einsatz Der Stoffwechselmessung in Der Fitnessbranche* (2010). Available at: http://www.telmed.de/files/siehe_zusammenfassung_diplomarbeit_gerhardt.pdf.
51. Borg G. Psychophysical Scaling With Applications in Physical Work and the Perception of Exertion. *Scand J Work Environ Health* (1990) 16 Suppl 1:55–8. doi: 10.5271/sjweh.1815
52. Löllgen H, Leyk D. Exercise Testing in Sports Medicine. *Dtsch Arztebl Int* (2018) 115:409–16. doi: 10.3238/arztebl.2018.0409
53. Scharhag-Rosenberger F. Spiroergometrie Zur Ausdauerleistungsdiagnostik. *Deutsche Z für Sportmedizin* (2010) 61:146–7.
54. Singh B, Spence RR, Sandler CX, Tanner J, Hayes SC. Feasibility and Effect of a Physical Activity Counselling Session With or Without Provision of an Activity Tracker on Maintenance of Physical Activity in Women With Breast Cancer - A Randomised Controlled Trial. *J Sci Med Sport* (2020) 23:283–90. doi: 10.1016/j.jsams.2019.09.019
55. Souweine J-S, Kuster N, Chenine L, Rodriguez A, Patrier L, Morena M, et al. Physical Inactivity and Protein Energy Wasting Play Independent Roles in Muscle Weakness in Maintenance Haemodialysis Patients. *PloS One* (2018) 13:e0200061. doi: 10.1371/journal.pone.0200061
56. Solomayer E-F, Braun E-M, Zimmermann JSM, Radosa JC, Stroeder J, Endrikat J, et al. Muscle Mass Loss in Patients With Metastatic Breast Cancer. *Arch Gynecol Obstet* (2019) 300:201–6. doi: 10.1007/s00404-019-05168-y
57. Kuo F-C, Lu C-H, Wu L-W, Kao T-W, Su S-C, Liu J-S, et al. Comparison of 7-Site Skinfold Measurement and Dual-Energy X-Ray Absorptiometry for Estimating Body Fat Percentage and Regional Adiposity in Taiwanese Diabetic Patients. *PloS One* (2020) 15:e0236323. doi: 10.1371/journal.pone.0236323
58. Busse M, Dräger M, Schätzel M, Thomas M, Schulze A, Falz R. Estimation of Subcutaneous Fat in Men – Part 1: Accuracy of 3 to 9 Point Measurements. *Clin Sports Med Int* (2013) 6:21–3.
59. Busse M, Schätzel M, Dräger M, Thomas M, Schulze A, Falz R. Estimation of Subcutaneous Fat in Men – Part 2: Comparison of Caliper and Ultrasound Measuring. *Clin Sports Med Int* (2013) 6:24–7.
60. Ketel IJG, Volman MNM, Seidell JC, Stehouwer CDA, Twisk JW, Lambalk CB. Superiority of Skinfold Measurements and Waist Over Waist-to-Hip Ratio for Determination of Body Fat Distribution in a Population-Based Cohort of Caucasian Dutch Adults. *Eur J Endocrinol* (2007) 156:655–61. doi: 10.1530/EJE-06-0730
61. Jackson AS, Pollock ML, Ward A. Generalized Equations for Predicting Body Density of Women. *Med Sci Sports Exerc* (1980) 12:175–81. doi: 10.1249/00005768-198023000-00009
62. Jabeen S, Espinoza JA, Torland LA, Zucknick M, Kumar S, Haakensen VD, et al. Noninvasive Profiling of Serum Cytokines in Breast Cancer Patients and Clinicopathological Characteristics. *Oncoimmunology* (2019) 8:e1537691. doi: 10.1080/2162402X.2018.1537691
63. Gustafson CE, Jadhav R, Cao W, Qi Q, Pegram M, Tian L, et al. Immune Cell Repertoires in Breast Cancer Patients After Adjuvant Chemotherapy. *JCI Insight* (2020) 5:134569. doi: 10.1172/jci.insight.134569
64. Spiliopoulou P, Gavriatopoulou M, Kastritis E, Dimopoulos MA, Terzis G. Exercise-Induced Changes in Tumor Growth *via* Tumor Immunity. *Sports (Basel)* (2021) 9:46. doi: 10.3390/sports9040046

65. Alberts E, Wall I, Calado DP, Grigoriadis A. Immune Crosstalk Between Lymph Nodes and Breast Carcinomas, With a Focus on B Cells. *Front Mol Biosci* (2021) 8:673051. doi: 10.3389/fmolb.2021.673051
66. Hanson ED, Bates LC, Harrell EP, Bartlett DB, Lee JT, Wagoner CW, et al. Exercise Training Partially Rescues Impaired Mucosal Associated Invariant T-Cell Mobilization in Breast Cancer Survivors Compared to Healthy Older Women. *Exp Gerontol* (2021) 152:111454. doi: 10.1016/j.exger.2021.111454
67. Robert Koch-Institut. Selen in Der Umweltmedizin: Mitteilung Der Kommission, Methoden Und Qualitätssicherung in Der Umweltmedizin. In: *Bundesgesundheitsbl - Gesundheitsforsch - Gesundheitsschutz*, vol. 49. Cham: Springer Nature (2006). p. 88–102. doi: 10.1007/s00103-005-1185-4
68. DiaSorin Inc. *LIAISON® 25 OH Vitamin D TOTAL Assay*. Available at: https://zentrallaborweb.uniklinikum-saarland.de/labor/data/Beipackzettel/Liaison/25DS6/Vitamin_D_2016-08.pdf (Accessed August 7, 2021).
69. Bittenbring JT, Neumann F, Altmann B, Achenbach M, Reichrath J, Ziepert M, et al. Vitamin D Deficiency Impairs Rituximab-Mediated Cellular Cytotoxicity and Outcome of Patients With Diffuse Large B-Cell Lymphoma Treated With But Not Without Rituximab. *J Clin Oncol* (2014) 32:3242–8. doi: 10.1200/JCO.2013.53.4537
70. Vaughan-Shaw PG, O'Sullivan F, Farrington SM, Theodoratou E, Campbell H, Dunlop MG, et al. The Impact of Vitamin D Pathway Genetic Variation and Circulating 25-Hydroxyvitamin D on Cancer Outcome: Systematic Review and Meta-Analysis. *Br J Cancer* (2017) 116:1092–110. doi: 10.1038/bjc.2017.44
71. Vinceti M, Filippini T, Del Giovane C, Dennert G, Zwahlen M, Brinkman M, et al. Selenium for Preventing Cancer. *Cochrane Database Syst Rev* (2018) 1: CD005195. doi: 10.1002/14651858.CD005195.pub4
72. Mao J, Yin H, Wang L, Wu J-Z, Xia Y, Zhu H-Y, et al. Prognostic Value of 25-Hydroxy Vitamin D in Extranodal NK/T Cell Lymphoma. *Ann Hematol* (2021) 100:445–53. doi: 10.1007/s00277-020-04320-y
73. Schindler TI, Wagner J-J, Goedicke-Fritz S, Rogosch T, Coccejus V, Laudenbach V, et al. TH17 Cell Frequency in Peripheral Blood Is Elevated in Overweight Children Without Chronic Inflammatory Diseases. *Front Immunol* (2017) 8:1543. doi: 10.3389/fimmu.2017.01543
74. Zamarron BF, Chen W. Dual Roles of Immune Cells and Their Factors in Cancer Development and Progression. *Int J Biol Sci* (2011) 7:651–8. doi: 10.7150/ijbs.7.651
75. Tsuda B, Miyamoto A, Yokoyama K, Ogiya R, Oshitanai R, Terao M, et al. B-Cell Populations Are Expanded in Breast Cancer Patients Compared With Healthy Controls. *Breast Cancer* (2018) 25:284–91. doi: 10.1007/s12282-017-0824-6
76. Gonzalez H, Hagerling C, Werb Z. Roles of the Immune System in Cancer: From Tumor Initiation to Metastatic Progression. *Genes Dev* (2018) 32:1267–84. doi: 10.1101/gad.314617.118
77. Wang L, Simons DL, Lu X, Tu TY, Avalos C, Chang AY, et al. Breast Cancer Induces Systemic Immune Changes on Cytokine Signaling in Peripheral Blood Monocytes and Lymphocytes. *EBioMedicine* (2020) 52:102631. doi: 10.1016/j.ebiom.2020.102631
78. Cossarizza A, Chang H-D, Radbruch A, Akdis M, Andrä I, Annunziato F, et al. Guidelines for the Use of Flow Cytometry and Cell Sorting in Immunological Studies. *Eur J Immunol* (2017) 47:1584–797. doi: 10.1002/eji.201646632
79. Varchetta S, Mele D, Oliviero B, Mantovani S, Ludovisi S, Cerino A, et al. Unique Immunological Profile in Patients With COVID-19. *Cell Mol Immunol* (2021) 18:604–12. doi: 10.1038/s41423-020-00557-9
80. Mazhari R, Brewster J, Fong R, Bourke C, Liu ZSJ, Takashima E, et al. A Comparison of non-Magnetic and Magnetic Beads for Measuring IgG Antibodies Against Plasmodium Vivax Antigens in a Multiplexed Bead-Based Assay Using Luminex Technology (Bio-Plex 200 or MAGPIX). *PloS One* (2020) 15:e0238010. doi: 10.1371/journal.pone.0238010
81. Gómez AM, Martínez C, Fiuza-Luces C, Herrero F, Pérez M, Madero L, et al. Exercise Training and Cytokines in Breast Cancer Survivors. *Int J Sports Med* (2011) 32:461–7. doi: 10.1055/s-0031-1271697
82. Tamayo-Velasco Á, Peñarrubia-Ponce MJ, Álvarez FJ, Gonzalo-Benito H, de la Fuente I, Martín-Fernández M, et al. Evaluation of Cytokines as Robust Diagnostic Biomarkers for COVID-19 Detection. *J Pers Med* (2021) 11:681. doi: 10.3390/jpm11070681
83. D Wild, R John, C Sheehan, S Binder, J He eds. The Immunoassay Handbook: Theory and Applications of Ligand Binding. In: *ELISA and Related Techniques*, *4th ed*. Oxford, Waltham, Amsterdam: Elsevier.
84. Zheng W, Flavell RA. The Transcription Factor GATA-3 Is Necessary and Sufficient for Th2 Cytokine Gene Expression in CD4 T Cells. *Cell* (1997) 89:587–96. doi: 10.1016/s0092-8674(00)80240-8
85. Hwang ES, Szabo SJ, Schwartzberg PL, Glimcher LH. T Helper Cell Fate Specified by Kinase-Mediated Interaction of T-Bet With GATA-3. *Science* (2005) 307:430–3. doi: 10.1126/science.1103336
86. Kanhere A, Hertweck A, Bhatia U, Gökmen MR, Perucha E, Jackson I, et al. T-Bet and GATA3 Orchestrate Th1 and Th2 Differentiation Through Lineage-Specific Targeting of Distal Regulatory Elements. *Nat Commun* (2012) 3:1268. doi: 10.1038/ncomms2260
87. Yakushina VD, Vasil'eva OA, Ryazantseva NV, Novitsky VV, Tashireva LA. The Effects of Galectin-1 on the Gene Expression of the Transcription Factors TBX21, GATA-3, FOXP3 and RORC. *Mol Cell Biochem* (2015) 398:245–9. doi: 10.1007/s11010-014-2227-8
88. Lin Z-W, Wu L-X, Xie Y, Ou X, Tian P-K, Liu X-P, et al. The Expression Levels of Transcription Factors T-Bet, GATA-3, Rorγt and FOXP3 in Peripheral Blood Lymphocyte (PBL) of Patients With Liver Cancer and Their Significance. *Int J Med Sci* (2015) 12:7–16. doi: 10.7150/ijms.8352
89. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* (1983) 67:361–70. doi: 10.1111/j.1600-0447.1983.tb09716.x
90. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. *J Natl Cancer Inst* (1993) 85:365–76. doi: 10.1093/jnci/85.5.365
91. Steyer R, Schwenkmezger P, Notz P, Eid M. Testtheoretische Analysen Des Mehrdimensionalen Befindlichkeitsfragebogen (MDBF). *Diagnostica* (1994) 40(4):320–8.
92. Tönnies S, Plöhn S, Krippendorf U. *Skalen Zur Psychischen Gesundheit (SPG). Testmanual*. Heidelberg: Roland Asanger Verlag (1996).
93. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring Fatigue and Other Anemia-Related Symptoms With the Functional Assessment of Cancer Therapy (FACT) Measurement System. *J Pain Symptom Manage* (1997) 13:63–74. doi: 10.1016/s0885-3924(96)00274-6
94. Roth AJ, Kornblith AB, Batel-Copel L, Peabody E, Scher HI, Holland JC. Rapid Screening for Psychologic Distress in Men With Prostate Carcinoma: A Pilot Study. *Cancer* (1998) 82:1904–8. doi: 10.1002/(sici)1097-0142(19980515)82:10<1904::aid-cncr13>3.0.co;2-x
95. Fayers P, Aaronson NK, Bjordal K, groenvold M, Curran D, Bottomley A. *EORTC QLQ-C30 Scoring Manual*. Brussels: European Organisation for Research and Treatment of Cancer (2001).
96. Mehnert-Theuerkauf A, Müller D, Lehmann C, Koch U. Die Deutsche Version Des NCCN Distress-Thermometers: Empirische Prüfung Eines Screening-Instruments Zur Erfassung Psychosozialer Belastung Bei Krebspatienten. *Z für Psychiatr Psychol und Psychotherapie* (2006) 54:213–23. doi: 10.1024/1661-4747.54.3.213
97. Riba MB, Donovan KA, Andersen B, Braun II, Breitbart WS, Brewer BW, et al. Distress Management, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* (2019) 17:1229–49. doi: 10.6004/jnccn.2019.0048
98. Yeh M-L, Chung Y-C, Hsu M-YF, Hsu C-C. Quantifying Psychological Distress Among Cancer Patients in Interventions and Scales: A Systematic Review. *Curr Pain Headache Rep* (2014) 18:399. doi: 10.1007/s11916-013-0399-7
99. Speed-Andrews AE, Courneya KS. Effects of Exercise on Quality of Life and Prognosis in Cancer Survivors. *Curr Sports Med Rep* (2009) 8:176–81. doi: 10.1249/JSR.0b013e3181ae98f3
100. Segal R, Zwaal C, Green E, Tomasone JR, Loblaw A, Petrella T. The Exercise for People With Cancer Guideline Development Group. Exercise for People With Cancer: A Systematic Review. *Curr Oncol* (2017) 24:290–315. doi: 10.3747/co.24.3619
101. Jackisch C, Kreienberg R, Blettner M, Harbeck N, Lück H-J, Haidinger R, et al. Assessment of Quality of Life in Postmenopausal Women With Early Breast Cancer Participating in the PACT Trial: The Impact of Additional Patient Information Material Packages and Patient Compliance. *Breast Care (Basel)* (2020) 15:236–45. doi: 10.1159/000500771

102. Lyman GH, Greenlee H, Bohlke K, Bao T, DeMichele AM, Deng GE, et al. Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline. *J Clin Oncol* (2018) 36:2647–55. doi: 10.1200/JCO.2018.79.2721
103. *NICE Guidline: Advanced Breast Cancer: Diagnosis and Treatment* (2009). Available at: https://www.nice.org.uk/guidance/cg81 (Accessed July 31, 2021).
104. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise Interventions on Health-Related Quality of Life for People With Cancer During Active Treatment. *Cochrane Database Syst Rev* (2012) 8: CD008465. doi: 10.1002/14651858.CD008465.pub2
105. Carayol M, Bernard P, Boiché J, Riou F, Mercier B, Cousson-Gélie F, et al. Psychological Effect of Exercise in Women With Breast Cancer Receiving Adjuvant Therapy: What Is the Optimal Dose Needed? *Ann Oncol* (2013) 24:291–300. doi: 10.1093/annonc/mds342
106. Minetto MA, Busso C, Gamerro G, Lalli P, Massazza G, Invernizzi M. Quantitative Assessment of Volumetric Muscle Loss: Dual-Energy X-Ray Absorptiometry and Ultrasonography. *Curr Opin Pharmacol* (2021) 57:148–56. doi: 10.1016/j.coph.2021.02.002
107. Ballesteros-Pomar MD, González-Arnáiz E, Pintor-de-la Maza B, Barajas-Galindo D, Ariadel-Cobo D, González-Roza L, et al. Bioelectrical Impedance Analysis as an Alternative to Dual-Energy X-Ray Absorptiometry in the Assessment of Fat Mass and Appendicular Lean Mass in Patients With Obesity. *Nutrition* (2021) 93:111442. doi: 10.1016/j.nut.2021.111442


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Oncology

SYSTEMATIC REVIEW
published: 12 November 2021
doi: 10.3389/fonc.2021.745280

# Physical Therapies for Psychosomatic Symptoms and Quality of Life Induced by Aromatase Inhibitors in Breast Cancer Patients: A Systematic Review and Meta-Analysis

*Xue-Ying Zhu[1], Zhong Li[1], Cong Chen[2], Ru-Li Feng[2], Bai-Ru Cheng[2], Ruo-Yi Liu[3], Rui-Ting Wang[2], Li Xu[4], Yue Wang[5], Xin Tao[6] and Peng Zhao[2]**

[1] Department of Oncology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China, [2] Department of Cardiology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China, [3] Department of Encephalopathy, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China, [4] Department of Gynecology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China, [5] Graduate School of Beijing University of Chinese Medicine, Beijing, China, [6] School of Medical Humanities, Capital Medical University, Beijing, China

OPEN ACCESS

**Edited by:**
Julio de la Torre,
Comillas Pontifical University, Spain

**Reviewed by:**
Marcus Vetter,
University Hospital of Basel, Switzerland
Marco Invernizzi,
University of Eastern Piedmont, Italy

***Correspondence:**
Peng Zhao
kyushuzhaopeng@hotmail.com

**Specialty section:**
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

**Received:** 21 July 2021
**Accepted:** 22 October 2021
**Published:** 12 November 2021

**Citation:**
Zhu X-Y, Li Z, Chen C, Feng R-L, Cheng B-R, Liu R-Y, Wang R-T, Xu L, Wang Y, Tao X and Zhao P (2021) Physical Therapies for Psychosomatic Symptoms and Quality of Life Induced by Aromatase Inhibitors in Breast Cancer Patients: A Systematic Review and Meta-Analysis. Front. Oncol. 11:745280. doi: 10.3389/fonc.2021.745280

**Objective:** To evaluate the effects of Physical Therapies (PTs) on improvement in psychosomatic symptoms and quality of life (QOL) in breast cancer patients.

**Data Sources:** Seven databases (MEDLINE, EMBASE, Cochrane CENTRAL, China National Knowledge Infrastructure, Wangfang, VIP, and China Biology Medicine disc databases) were systematically searched from the database inception through May 18, 2021.

**Study Selection:** Randomized controlled trials (RCTs) which compared acupuncture or exercise with a sham control or usual care for the treatment of aromatase inhibitors (AIs)-related psychosomatic symptoms and QOL.

**Data Extraction and Synthesis:** Data were screened and extracted independently using predesigned forms. The quality of RCTs was assessed with the Cochrane Handbook for Systematic Reviews of Interventions. The effect size was calculated *via* random-effects modeling. The quality of evidence was evaluated with the Grading of Recommendations Assessment, Development and Evaluation approach.

**Main Outcomes and Measures:** The score of pain was measured with BPI scale and Western Ontario and the McMaster Universities Index (WOMAC) scale. Emotional state was measured with Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS-A), and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue). The QOL score was measured by self-reported measurements, including the Functional Assessment of Cancer Therapy-General (FACT-G) scale and 36-Item Short Form Survey (SF-36) scale.

**Results:** Eleven RCTs (with 830 patients) were included in the systematic review, and data from 10 RCTs (with 798 patients) were used in the meta-analysis. Results showed acupuncture significantly reduced worst pain scores ($P < 0.00001$, $I^2 = 83.5\%$) [SMD = –0.81, 95% CI (–1.51, –0.11)], but the effect of exercise therapies was not significant in overall change in worst pain scores ($P = 0.006$, $I^2 = 72.3\%$) [SMD = –0.30, 95% CI (–0.76, 0.16)]. Both acupuncture and exercise resulted in little to no difference in overall change in HADS-A subscale (P = 0.026<0.05, $I^2 = 79.8\%$) [WMD = –0.21, 95% CI (–3.44, 3.03)], PSQI subscale (P = 0.488, $I^2 = 0\%$) [WMD = 0.98, 95% CI (–0.57, 2.53)], and FACIT-Fatigue subscale (P = 0.022<0.05, $I^2 = 81.0\%$) [WMD = 1.6, 95% CI (–5.75, 8.94)]. Exercise (compared with usual care) was associated with improving overall change in health-related QOL (subscales of SF-36 tool) (P = 0, $I^2 = 72.1\%$) [WMD = 7.97, 95% CI (5.68, 10.25)] and cancer-specific QOL (subscales of FACT-G tool) (P = 0.304, $I^2 = 16\%$) [WMD = 1.16, 95% CI (0.34, 1.97)].

**Conclusions and Relevance:** This systematic review and meta-analysis suggested that based on moderate-level evidence, acupuncture was associated with significant reductions in pain intensity, and exercise might improve QOL in breast cancer patients treated with AIs. However, in psychosomatic symptoms such as anxiety, sleep disturbance, and fatigue, acupuncture and exercise training did not result in significant improvements.

**Keywords: physical therapies, acupuncture, exercise, breast cancer, aromatase inhibitors, pain, quality of life**

## 1 INTRODUCTION

The number of breast cancer survivors is increasing as breast cancer becomes a major health concern worldwide (1). According to statistics from 185 countries in 2018, nearly 2.1 million cases of breast cancer were newly diagnosed (2). It was estimated that about 15.1% of the new cases of cancer were breast cancer, with an estimated 2.5 million new cases in China each year (3). Advances in clinical management of breast cancer increase survival rate and also cause cancer-related side effects, critically impacting on physical, psychological, and spiritual aspects of QOL (4). Endocrine therapy, especially aromatase inhibitors (AIs), is the main standard treatment for hormone-receptor-positive breast cancer (5). Eighty percent of breast cancer is hormone receptor–positive breast cancer, including progesterone receptor (PR)-positive or/and estrogen receptor (ER)-positive subtypes (6). While five years of AIs therapy can improve disease-free survival (DFS) and breast cancer specific survival (BCSS) for postmenopausal patients in an early stage of the cancer, these inhibitors are associated with several sequelae, among which is the worsening of psychosomatic symptoms (7).

AIs may induce disorders in joint and muscle, known as aromatase inhibitor-induced musculoskeletal symptoms (AIMSS), which manifest as symmetric pain or soreness in multiple joints and morning stiffness (8, 9). Psychosomatic factors play an important role in pain and physical disabilities (10). Physical symptoms such as depression can lead to chronic pain and require multiple treatment (11). Serotonin and norepinephrine influence both the progress of depression and pain because of the same neurochemical pathway. Therefore, depression and associated painful physical symptoms must be treated with equal attention (12). Illness and treatment-related distress always plagued most breast cancer patients, such as changes in body image and sexuality and fear of recurrence (13). Compared with other cancer types, breast cancer survivors showed more serious psychiatric comorbidity and psychosocial distress especially anxiety and adjustment disorders (14). In general, AIs are effective drugs for breast cancer with minimal adverse effects, including hot flashes, vaginal dryness, and headache, which are typically mild (15). However, postmenopausal breast cancer patients affected by comorbidities and treatments including estradiol reduction and cytokine dysregulation are likely to contribute to deteriorated psychosomatic symptoms, such depression and anxiety (16, 17). The abovementioned side effects strike the treatment adherence of AIs, despite the survival advantage of AIs.

In the face of the variety of psychosomatic symptoms, breast cancer patients with AIs are complex and heterogeneous. To date, no definitive pharmacological therapy has been confirmed to avoid unfavorable side effects (18). In order to meet the rehabilitation needs caused by psychosomatic symptoms, related alternative approaches have received much attention (19, 20). In recent years, physical therapy (PT) has been used to treat side effects caused by AIs (7, 21). PT is generally divided into two types: one based on using physical factors as the main means, including biofeedback and acupuncture; the other on functional training, known as the exercise therapy

including yoga, aquatic exercise, tai-chi, walking, Pilates, and resistance exercises (22). Although PT, such as acupuncture, exercise, or yoga, has been shown to improve AIMSS and health-related QOL to some extent in previous published studies (18, 21, 23), the effects of PT on psychosomatic symptoms were not assessed.

Psychosomatic symptoms play a key role in the management of patients with breast cancer treated with AIs. Studies have shown that a large number of patients with AIs have poor compliance, which may impact their survival (24). To evaluate the efficacy of PT in the treatment of psychosomatic symptoms, this systematic review focuses on the psychosomatic symptoms of PT in breast cancer survivors, summarizing and evaluating the evidence from all available randomized controlled trials (RCTs) to obtain relatively robust clinical evidence.

# 2 METHODS

## 2.1 Search Strategy

Seven databases (MEDLINE, EMBASE, Cochrane CENTRAL, China National Knowledge Infrastructure, Wangfang, VIP, and China Biology Medicine disc databases) were systematically searched from the database inception through May 18, 2021. The literature lists of relevant review articles and full-text review papers were also cross-checked by different reviewers. The search strategy involved four parts: clinical situation (breast cancer and AIs), intervention (physical therapy), outcomes (psychosomatic symptoms), and study type (randomized controlled trial). The complete search strategies for all the databases can be found in **Supplement 1**. Moreover, the reference review articles, conference summary, and comments on supplementary citations were scrutinized. All the studies included were limited to humans, and there was no language restriction.

## 2.2 Inclusion and Exclusion Criteria

To prevent bias, the inclusion criteria were prespecified according to population, intervention, comparison, and outcome (PICO terms): (P) Types of participants: Participants had a diagnosis of stage I to III ER-positive, or PR-positive breast cancer in accordance with diagnostic criteria (25) and were receiving adjuvant therapy for AIs; (I) Types of interventions: All types of management interventions for psychosomatic symptoms were considered; acupuncture of all types, doses, and courses, and all exercise therapy, which had to meet the definition of "physical activity that is planned, structured and repetitive and has a final or intermediate objective of the improvement or maintenance of physical fitness," (26) such as tai chi, yoga, aqua aerobics, and resistance exercise. These exercise programs had aerobic/endurance, stretching/flexibility, resistance/strengthening, or combined training as a key component and resulted in significant physiological changes; (C) Types of studies: All RCTs or quasi-experimental studies which examined the effectiveness of all kinds of PTs on AIMSS or psychosomatic symptoms in AIs treated patients with breast cancer; (O) Types of outcome measures:

### 2.2.1 Primary Outcomes

Pain (subgroup scores of AIMSS including three types of symptoms: pain, stiffness, and grip strength). The score of pain should be measured using scales including the BPI scale, Western Ontario and McMaster Universities Index (WOMAC) scale, VAS scale, and electronic algometer.

Emotional states (including anxiety, depression, sleep disturbance, or fatigue). Emotional state should be measured by standard measurements such as Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS-A), and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue).

### 2.2.2 Secondary Outcomes

The QOL score should be measured by self-reported measurements, including the Functional Assessment of Cancer Therapy-General (FACT-G) scale and 36-Item Short Form Survey (SF-36) scale.

The exclusion criteria were prespecified as follows: (1) Not RCT studies such as small case series, protocols, and reviews; (2) Combined use of drugs; (3) No control group or one arm; (4) Duplicate publication; (5) Women with advanced/metastatic breast cancer; and (6) Animal and *in vitro* studies.

## 2.3 Data Extraction and Risk of Bias Assessment

All data were extracted independently by two reviewers, and discrepancies were discussed with the third reviewer. Predesigned forms included study features (name of the first author, year of publication, sample size, and median age), clinical characteristics (participants, interventions, treatment groups, and outcome measures), treatment details, methodological characteristics, and significant results. Two evaluators independently assessed the quality of included studies according to the Cochrane risk-of-bias tool for randomized trials (RoB2). Disagreements were resolved through discussion with another reviewer until consensus was reached. Each study was assigned a low, high, or some concerns risk of bias for six specific areas (the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results, and other bias), using information extracted from the papers and supplementary materials and contacting the study authors when needed. The overall evidence and certainty of evidence were evaluated with the Grading of Recommendations Assessment, Development, and Evaluation approach.

## 2.4 Statistical Analyses

Studies with needed data were included in meta-analysis using random- or fixed-effects model according to their effect size to calculate risk ratio and 95% CI. The heterogeneity between trials was determined by $\chi^2$ test and reported as $I^2$. Statistical analyses were performed within Cochrane Program Review Manager Version 5.3 (Cochrane Collaboration, Oxford, UK). Two-sided $P < 0.05$ was considered statistically significant. Studies were grouped according to the type of intervention and the comparator (sham treatment). For studies with multiple control groups, such as real acupuncture *versus* sham

acupuncture *versus* wait-list control, the results were divided into pairwise comparisons according to different comparators. When different results of the same study were reported in different publications, the data were merged. Subgroup sensitivity analyses were conducted to explore potential sources of heterogeneity.

# 3 RESULTS

## 3.1 Search Results

A total of 1,836 articles were identified by searching the seven databases, from which six articles (0.3%) came from other sources, such as bibliography and citation searching. After 596 duplicate publications (32%) had been removed, 1,240 records (68%) went through title and abstract screening, after which 1,229 articles (67%) were excluded because they did not meet the inclusion criteria. Eleven studies were included in the systematic review or qualitative synthesis (27–39). One study (9%) (38) was excluded from the meta-analysis as it had incomplete data, and we failed to contact the authors for the missing data. Quantitative synthesis was performed with 10 trials (91%). More details of the process can be found in the study flow diagram (**Figure 1**) (40).

## 3.2 Study Characteristics

### 3.2.1 Basic Characteristics

Among the 11 clinical trials included, five (45%) were sham controlled (27–30, 37) and six (54%) were open label-controlled trials (31–36). Nine studies (81%) applied a two-group parallel control design, and two studies applied a three-group parallel control design. Five studies (45%) evaluated the efficacy of manual acupuncture and electroacupuncture (27–30, 37), and six (54%) compared different exercise therapies with usual care (31–36). Seven studies (63%) were conducted in United States (27, 29, 30, 33, 34, 36, 37), two (18%) in Australia (32, 38), and one (9%) in Brazil and United Kingdom (32, 35). The study characteristics are shown in **Table 1**.

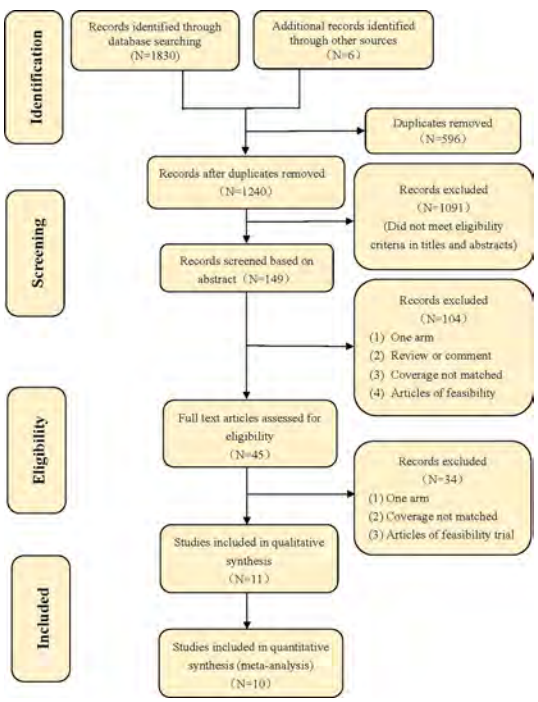



**FIGURE 1** | Flow diagram.

### 3.2.2 Population

A total of 830 patients were enrolled in the 11 studies, and 10 studies with 795 patients were included in the meta-analysis. The sample sizes included in the studies ranged from 29 to 226, with 387 participants (49%) in the acupuncture trials (27–30, 37–39) and 411 (51%) in the exercise trials (31–36). Eleven studies reported the mean ages of participants, ranging from 57 to 66 years (27, 29–37), and one study reported age ranges (38). At the time of enrolment, all participants were using AIs, including anastrozole, letrozole, exemestane, etc. Nine studies (81%) reported the patients were diagnosed with breast cancer (staged as I–III), and six studies (54%) (29, 30, 33, 36–38) reported the patients were postmenopausal. The dropout rate of four studies (36%) was zero (31, 34, 35, 38). Some studies reported that their inclusion criteria were women who experienced any joint symptoms while taking AIs, and eight studies (72%) set the minimum pain score that met the inclusion criteria (27, 29, 30, 33, 34, 36–38).

### 3.2.3 Interventions

The interventions included acupuncture [manual acupuncture (29, 30, 37, 39) and electroacupuncture (27, 38)], exercise (magnitude vibrative (31), walking (34, 35), and training [32, 33, 36)], sham acupuncture, and no treatment. Four studies (36%) used acupuncture therapy twice a week for 30 min for 2 to 6 weeks (27, 30, 37, 38), and one study (9%) used acupuncture therapy eight times a week for 8 weeks (29). Two studies (18%) surveyed walking plans, one of which was Nordic walking, which utilizes walking with hand-held poles (35). Another walking study was based on a family exercise program, walking 150 min a week (34). Three studies (27%) used a combination of resistance training plus aerobic exercise (32, 33, 36). The intervention time of each study is different, ranging from 6 weeks to 12 months. There were different reports on the intensity of exercise intervention. One study (9%) reported the ideal exercise intensity level, with a target of 60 to 80% of the maximum heart rate, based on the $VO_2$ maximum test (36). The majority of studies included at least 150 to 200 min of exercise per week.

### 3.2.4 Outcomes

Pain was one of the most important components of psychosomatic symptoms. In five studies (45%), the BPI scale was used to assess the worst pain, worst stiffness, and pain severity associated with AIMSS in patients diagnosed with breast cancer (28, 30, 35–37). In five studies (45%), the WOMAC was used to assess the severity of knees or hips osteoarthritis (28, 31, 34, 36, 37). The global score of the PSQI was used to measure sleep condition in two studies (18%) (27, 29). Anxiety was assessed with the anxiety subscale of the HADS-A in two studies (18%) (27, 29).

**TABLE 1** | Characteristics of trials included in the analysis.

| Source* | Intervention | Trial design | Sample size (I/C)[a], dropout (I/C)[a] | Age (I/C)[a] (year) | Arms (course) | Participant characteristics | Race | Outcome measurement tool | Primary outcome result |
|---|---|---|---|---|---|---|---|---|---|
| Crew et al. (37) **(US)** | MA | Sham-controlled 2-arm | 43 (23/20), 5 (3/2) | 58 (44–77)/57 (37–77) | TA/SA (30 min twice weekly, 6 wk) | 1. Postmenopausal<br>2. Stage I–III breast cancer<br>3. Estrogen receptor-positive, progesterone receptor-positive, or both<br>4. AI for 3 months<br>5. Pain score on the BPI-SF of ≥3 points | White (39%), Hispanic (55%), Black (3%), Asian (3%) | 1. BPI-SF<br>2. WOMAC<br>3. M-SACRAH<br>4. FACT-G | Positive |
| Oh et al. (38) **(Australia)** | EA | Sham-controlled 2-arm | 32 (16/16), 3 (2/1) | <45 14 (93%) and ≥45 1 (7%)/<45 12 (86%) and ≥45 2 (14%) | TA/SA (30 min twice weekly, 6 wk) | 1. Postmenopausal<br>2. Stage I–IIIa breast cancer<br>3. Estrogen receptor-positive, progesterone receptor-positive, or both<br>4. AI for 6 months<br>5. Pain score on the BPI-SF of points | Caucasian (86%), Others (14%) | 1. BPI-SF<br>2. WOMAC<br>3. FACT-G<br>4. Blood analysis: CRP, ESR | Positive |
| Mao et al. (27) **(US)**[b] | EA | Sham-controlled 3-arm | 67 (22/22/23), 8 (3/3/2) | 57.5 ± 10.1/60.9 ± 6.5/60.6 ± 8.2 | TA/SA/WLC (twice a week for 2 wk; then weekly for 6 wk) | 1. Stage I–III breast cancer<br>2. AI for 3 months<br>3. Joint pain ≥3 months<br>4. Numerical rating scale ≥4 points<br>5. At least15 days with pain in the preceding 30 days | White (72%), Others (28%) | 1. BPI<br>2. WOMAC<br>3. DASH<br>4. PPT<br>5. Fatigue: BFI<br>6. Sleep: PSQI<br>7. Anxiety: HADS<br>8. Depression: HADS-Depression | Positive[c] |
| Bao et al. (29) **(US)**[b] | MA | Sham-controlled 2-arm | 51 (25/26), 4 (2/2) | 61 (44–82)/61 (45–85) | TA/SA (8 weekly for 8 wk) | 1. Postmenopausal<br>2. Stage I–III breast cancer<br>3. AI for 1 month<br>4. Baseline HAQ-DI score ≥3 and/or pain using a 100-point VAS ≥20<br>5. Have not received acupuncture treatment in the past 12 months | Caucasian (72%), African American (19%), Other (9%) | 1. HAQ-DI<br>2. VAS<br>3. β-endorphin; estradiol; Proinflammatory cytokines: IL-1, -6, -8, -10, -12, -17, IFN-γ, TNF-α<br>4. Menopausal symptoms: NSABP<br>5. Hot Flash: HFRDI<br>6. Sleep: PSQI<br>7. Depression: CESD<br>8. Anxiety:HADS-A, Quality of life: Euro Qol | Negative |
| Hershman et al. (30) **(US)** | MA | Sham-controlled 3-arm | 226 (110/59/57), 20 (9/5/6) | 60.8 (34.1–80.6)/57.0 (40.6–77.5)/60.6 (27.1–76.0) | TA/SA/WLC (twice a week for 6 wk; then weekly for 6 wk) | 1. Postmenopausal or premenopausal with gonadotropin-releasing hormone agonist<br>2. Stages I–III breast cancer | White (85%), Black (4.4%), Asian (6.6%), Pacific Islander (0.4%), American Indian (0.4%), others (3.2%) | 1. BPI<br>2. WOMAC<br>3. PROMIS PI-SF<br>4. M-SACRAH<br>5. FACT-ES | Positive[c] |

*(Continued)*

**TABLE 1** | Continued

| Source* | Intervention | Trial design | Sample size (I/C)[a], dropout (I/C)[a] | Age (I/C)[a] (year) | Arms (course) | Participant characteristics | Race | Outcome measurement tool | Primary outcome result |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 3. Estrogen receptor-positive, progesterone receptor-positive, or both<br>4. AI ≥ 1 month to continue for at least 1 additional year<br>5. Zubrod performance 0–1<br>6. Pain score on the BPI-SF of ≥3 points | | | |
| Baker et al. (31) **(Australia)** | EX (Low-frequency, low-magnitude vibrative) | Open label-controlled 2-arm | 31 (14/17), 0 | 61.6 ± 9.2/61.6 ± 7.8 | EX/WLC (20 min of vibration, 3 weekly for 12 wk) | 1. Breast cancer (stage unknown)<br>2. Taking any bone-altering medications or supplements<br>3. Able to stand unassisted for sustained periods of time (i.e., 20 min) | Australian (100%) | 1. WOMAC<br>2. FACT–Fatigue subscale<br>3. Bone Resorption and Formation: NTx/Cr, P1NP<br>4. Body Composition and Bone Mineral Density<br>5. Physical Functioning | Negative |
| Paulo et al. (32) **(Brazil)** | EX (resistance training followed by aerobic training) | Open label-controlled 2-arm | 36 (18/18), 7 (3/4) | 63.2 ± 7.1/66.6 ± 9.6 | EX/CG (3 weekly for 36 months) | 1. Aged between 50 and 80 years<br>2. Stage I–III breast cancer<br>3. AI for breast cancer<br>4. No muscle and bone damage | Brazilians (100%) | 1. SF36<br>2. EORTC QLQ-C30<br>3. EORTC QLQ-BR23 | Positive |
| Baglia et al. (33) **(US)** | EX (strength-training and aerobic exercise) | Open label-controlled 2-arm | 121 (61/60), 38 (16/22) | 62 ± 7/60.5 ± 7 | EX/CG (2 weekly for 12 months) | 1. Postmenopausal women, HR-positive, stage I–III BC diagnosed 0.5–4 years prior to enrolment<br>2. AI for 6 months<br>3. Arthralgias for ≥2 months, with BPI-SF score≥3/10<br>4. 4.Pre-existing joint pain allowed if worsened after AI<br>5. Physically inactive: baseline <90 min exercise/week, no strength training | Non-Hispanic White (85%)<br>Hispanic (3%)<br>African American (9%)<br>Asian/Pacific Islander (2%)<br>American Indian (1%) | 1. FACT<br>2. FACT-G<br>3. FACT-B<br>4. SF-36<br>5. FACIT-Fatigue | Positive |
| Nyrop et al. (34) **(US)** | EX (Walk) | Open label-controlled 2-arm | 62 (31/31), 9 (7/2) | 63.3 ± 6.9/64.4 ± 9.7 | EX/WLC (150 min weekly for 6 wk) | 1. Age >21 years<br>2. Stage 0–III breast cancer<br>3. AI for 4 weeks<br>4. Pain score on the BPI-SF of ≥3 points | Caucasian (74%), Others (26%) | 1. VAS<br>2. WOMAC<br>3. FACT-G<br>4. RAI<br>5. ASE<br>6. OEE<br>7. SEPA | Positive |

*(Continued)*

**TABLE 1** | Continued

| Source* | Intervention | Trial design | Sample size (I/C)[a], dropout (I/C)[a] | Age (I/C)[a] (year) | Arms (course) | Participant characteristics | Race | Outcome measurement tool | Primary outcome result |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 5. Exercising ≤150 min per week | | | |
| Fields et al. (35) **(UK)** | EX (Nordic walking) | Open label-controlled 2-arm | 40 (20/20), 0 | 60 ± 8/66 ± 7 | EX/CG (once a week for 6 wk, then four times a week for 6 wk) | 1. Breast cancer (stage unknown)<br>2. AI for breast cancer<br>3. Reporting joint symptoms over preceding 12 months | Caucasian (100%) | 1. BPI-SF<br>2. PSEQ<br>3. CES-D<br>4. SF-36 | Positive |
| Irwin et al. (36) **(US)** | EX (strength-training and aerobic exercise) | Open label-controlled 2-arm | 121 (61/60), 38 (16/22) | 62 ± 7/60.5 ± 7 | EX/CG (2 weekly for 12 months) | 1. Postmenopausal women, HR-positive, stage I–III BC diagnosed 0.5–4 years prior to enrolment<br>2. AI for 6 months<br>3. Arthralgias for ≥2 months, with BPI-SF score≥3/10<br>4. Pre-existing joint pain allowed if worsened after AI<br>5. Physically inactive: baseline <90 min exercise/week, no strength training | Non-Hispanic White (85%)<br>Hispanic (3%)<br>African American (9%)<br>Asian/Pacific Islander (2%)<br>American Indian (1%) | 1. BPI<br>2. WOMAC<br>3. DASH<br>4. Grip strength | Positive |

**Sources of funding for the included studies are provided in the **Supplement 1**.*

*[a]I/C, data of Intervention group/data of control group(s);*

*[b]Different outcomes were reported in separate publications; the data were merged.*

*[c]Primary results of comparisons (experimental intervention vs. sham control(s) and experimental intervention vs. waitlist control) were both positive.*

*NM, no mention; EA, electroacupuncture; MA, manual acupuncture; AI, aromatase inhibitor; TA, true acupuncture group; SA, sham acupuncture group; WLC, waitlist control; EX, exercise; CG, control group; BPI-SF, Brief Pain Inventory–Short Form; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; M-SACRAH, Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands; FACT-G, Functional Assessment of Cancer Therapy–General; BFI, Brief Fatigue Inventory; PSQI, Pittsburgh Sleep Quality Index; HADS, Hospital Anxiety and Depression Scale; HAD-DI, The Health Assessment Questionnaire—the disability index; NSABP, National Surgical Adjuvant Breast and Bowel Project; HADS-A, Hospital Anxiety and Depression Scale—the anxiety subscale; PROMIS PI-SF, The PROMIS Pain Impact-Short Form; CES-D, Center for Epidemiological Studies Depression; PSEQ, Pain Self-Efficacy Questionnaire; DASH, The Disabilities of the Arm, Shoulder, and Hand questionnaire; PPT, The Physical Performance Test; BMI, body mass index; % FM, percent body fat; LBM, lean body mass; BMD, bone mineral density; FSI, Fatigue Symptom Inventory; AUSCAN, Australian/Canadian Hand Osteoarthritis Index; HFRDIS, Hot Flash Related Daily Interference Scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer questionnaire entitled "Quality of life Questionnaire version 3.0; EORTC QLQ-BR23, European Organization for Research and Treatment of breast cancer module; FACT-ES, Functional Assessment of Cancer Therapy—the endocrine subscale; FACT-B, Functional Assessment of Cancer Therapy–Breast cancer; FACIT-Fatigue, Functional Assessment of Chronic illness Therapy–Fatigue; SF-36, the MOS item short from health survey; VAS, visual analog scale; RAI, rheumatology attitudes index; ASE, arthritis self-efficacy scale; OEE, outcome expectations from exercise; SEPA, self-efficacy for physical activity.*

FACIT-Fatigue is a 13-item subscale to assess fatigue-related concerns in two studies (18%) (31, 33). QOL was measured by the FACT-G questionnaires in two studies (18%) (33, 34) and SF-36 in three studies (27%) (32, 33, 35).

## 3.3 Methodological Quality of Clinical Studies

Details of the risk assessment of bias in the included studies are documented in **Figure 2**. Four studies (36%) (27, 29, 30, 36, 37) were of high quality. Because of the nature of the exercise intervention, it was not practical to ensure blindness of participants and outcome assessors. However, the measurements of psychosomatic symptoms were always the result of the patients' reported outcomes. Therefore, detection bias was objectively presented when participants and outcome assessors could not be blinded to the intervention. Thus, the five open-label studies (45%) (31–35) without sham exercises were rated as having a high or some concerns risk of bias for blinding of the participants and outcome assessors. One study (9%) (34) reported randomization errors, and although the cause and time of the error were not reported, we judged it to be a high-risk selection bias (random and allocation concealment). One study did not use appropriate analysis to estimate the effect of assignment to intervention, and we judged (9%) (35) it to be a high-risk selection bias (deviations from the intended interventions). Details of this study are presented in the **Supplement 1**.

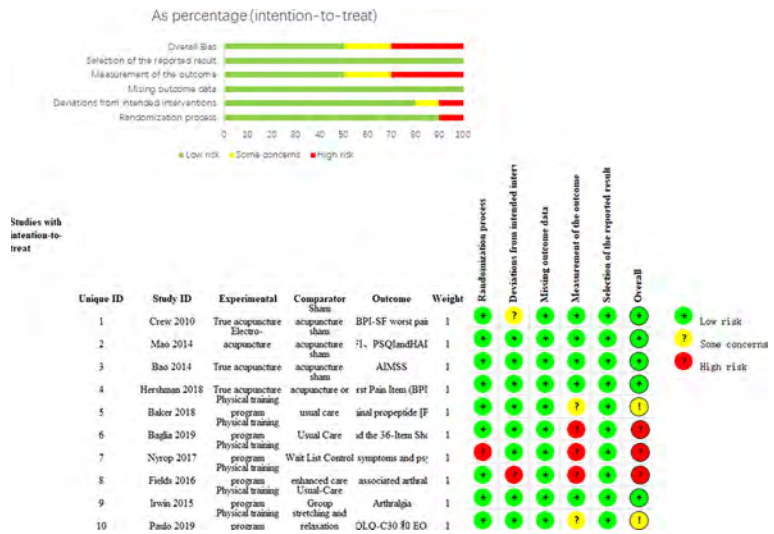



**FIGURE 2** | Each "Risk of bias" item for each included study.

## 3.4 Outcomes of Acupuncture and Exercise

### 3.4.1 Interventions of Pain

Seven studies used outcomes reported by participants to assess pain symptoms (28, 30, 37), which included the BPI scale and WOMAC. The BPI scale is composed of three subscales: pain-related interference, pain severity, and worst pain. In acupuncture trials (28, 30, 37), three subscales were analyzed, but in exercise trials (35, 36), only analyzed one subscale of worst pain. WOMAC is composed of four subscales: the pain, stiffness, function (difficulty), and normalized subscales. In the meta-analysis of acupuncture and exercise trials, we only included the pain subscale of WOMAC to assess the effect of interventions.

*Acupuncture.* We performed a meta-analysis on the effect of acupuncture on worst pain. Because of the different scoring systems, SMD was used. In the meta-analysis, two studies (30, 37) used the BPI worst pain scores and two studies (28, 37) used the WOMAC pain subscale. Given the high heterogeneity of the four studies ($p < 0.00001$, $I^2 = 83.5\%$), we used a random-effects model in the combined effects analysis. The true-acupuncture (c) group was better than the sham-acupuncture (SA) group [SMD = −0.81, 95% CI (−1.51, −0.11)] (**Figure 3**). The significant heterogeneity might result from the diversity of outcome assessment tools and acupuncture interventions used in the studies.

Two studies were included in the meta-analysis on BPI Pain Severity score (28, 30). Because of the high heterogeneity (P=0.015 < 0.05, $I^2 = 71.5\%$), we divided them into two subgroups according to the control method used. No significant differences were observed between the TA group and SA group (P = 0.736, $I^2 = 0\%$) [WMD = −0.53, 95% CI (−1.06, 0)], while there were also no significant differences between the TA group and waitlist control (WLC) group (P = 0.187, $I^2 = 42.5\%$) [WMD = −1.70, 95% CI (−2.43, −0.98)] (**Figure 4**). Three studies were included in the meta-analysis on BPI Pain-Related Interference score (28, 30, 37). Because of the high heterogeneity (P=0.116, $I^2 = 45.9\%$), we divided them into two subgroups based on the control method used. There were no significant differences between the TA group and SA group (P = 0.141, $I^2 = 49.0\%$) [WMD = −0.87, 95% CI (−1.78, 0.06)], while there were also no significant differences between the TA group and waitlist control (WLC) group (P = 0.254, $I^2 = 23.1\%$) [WMD = −1.34, 95% CI (−2.12, −0.56)] (**Figure 5**).

*Exercise.* The effect of exercise on pain was performed by using BPI worst pain scores and WOMAC pain subscale. Because of the different scoring systems, SMD was used. In the meta-analysis, two studies (35, 36) used the BPI worst pain scores and three studies (31, 34, 36) used the WOMAC pain subscale. Considering the high heterogeneity of these five studies (P =0.006, $I^2 = 72.3\%$), we adopted a random-effects model in the comprehensive effects analysis. There were no significant differences between the exercise group and the control group (P =0.006, $I^2 = 72.3\%$) [SMD = −0.30, 95% CI (−0.76, 0.16)] (**Figure 6**). The considerable statistical heterogeneity of studies in the meta-analysis might result from the range of exercise interventions utilized between the studies and the wide range of outcome assessment tools used. Due to the lack of available data, the other subscales were not analyzed in exercise trials.

### 3.4.2 Interventions of Anxiety, Sleep Disturbance, and Fatigue

*Acupuncture.* The effect of acupuncture on anxiety and sleep disturbance was performed in a meta-analysis by using HADS-A and PSQI. In the meta-analysis, two studies used the HADS-A subscale (27, 29). Because of the high heterogeneity, we used a random-effects model. There were no significant differences between the TA group and the SA group (P = 0.026<0.05, $I^2 = 79.8\%$) [WMD = −0.21, 95% CI (−3.44, 3.03)] (**Figure 7**).

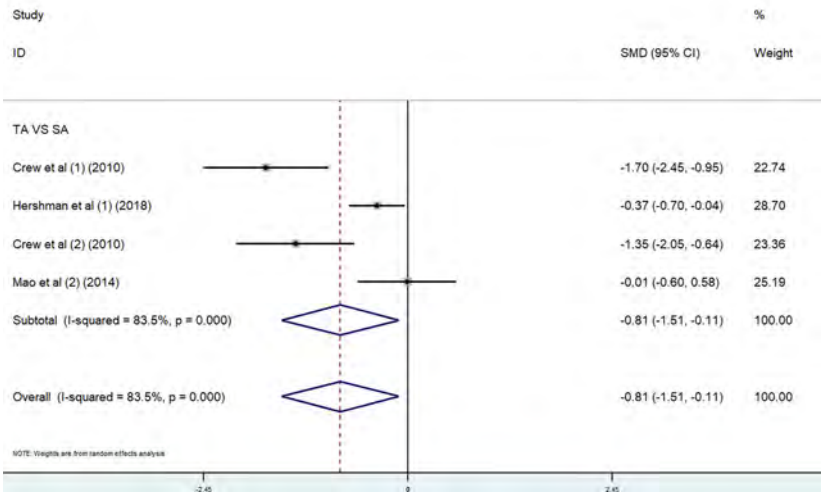



**FIGURE 3** | Overall change of acupuncture trials in pain, combined using (1) BPI worst pain subscale and (2) WOMAC pain subscale.

Two studies were included in the meta-analysis on PSQI subscale (27, 29). Because of the low heterogeneity, we used a fixed-effects model. There were also no significant differences between the TA group and the SA group (P = 0.488, $I^2$ = 0%) [WMD = 0.98, 95% CI (−0.57, 2.53)] (**Figure 8**).

*Exercise.* The effect of exercise on fatigue was performed in a meta-analysis by using FACIT-Fatigue. In the meta-analysis, two studies used the FACIT-Fatigue subscale (31, 33). Because of the high heterogeneity, we used a random-effects model. There were no significant differences between the exercise group and the control group (P = 0.022<0.05, $I^2$ = 81.0%) [WMD = 1.6, 95% CI (−5.75, 8.94)] (**Figure 9**).

### 3.4.3 Interventions of QOL

*Exercise.* Three studies used SF-36 to assess health-related QOL (32, 33, 35). The subscales of SF-36 can be grouped into a Physical Component Score and a Mental Health Component Score. The higher the score, the better the health status. Using a random-effects model, the results are from eight subscales: role physical (P = 0.05, $I^2$ = 66.6%) [WMD = 10.55, 95% CI (0.83, 20.27)]; physical functioning (P = 0.066, $I^2$ = 63.6%) [WMD = 12.11, 95% CI (4.63, 19.59)]; body pain (P = 0, $I^2$ = 91.3%) [WMD = 13.59, 95% CI (−3.44, 30.61)]; general health (P = 0.394, $I^2$ = 0%) [WMD = 4.31, 95% CI (1.83, 6.79)]; vitality (P = 0, $I^2$ = 87.3%) [WMD =9.79, 95% CI (−3.09, 22.68)];

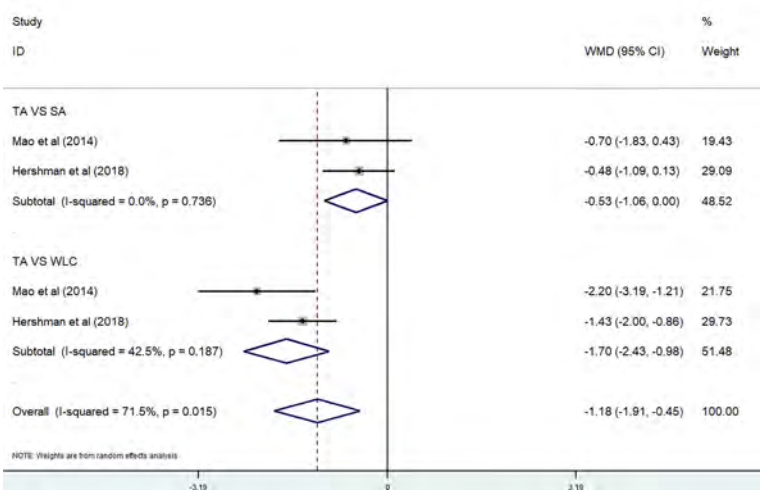



**FIGURE 4** | BPI Pain Severity score in acupuncture trials.

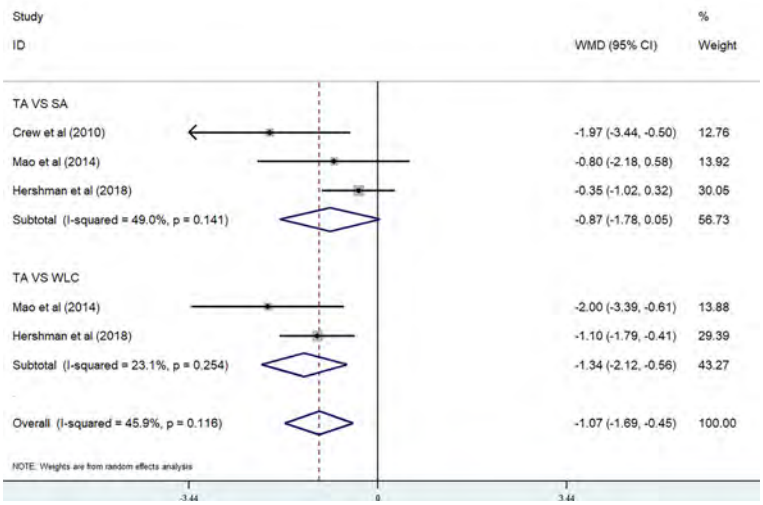



**FIGURE 5** | BPI Pain-Related Interference score in acupuncture trials.

social functioning (P = 0.021, $I^2$ = 74.1%) [WMD = 7.16, 95% CI (−1.20, 15.52)]; emotional role (P = 0.582, $I^2$ = 0%) [WMD = 2.51, 95% CI (−1.90, 6.92)], and mental health (P = 0.945, $I^2$ = 0%) [WMD = 3.21, 95% CI (0.8, 5.62)]. The overall result of meta-analysis showed the effect of exercise resulted in improvements in health-related QOL (P = 0, $I^2$ = 72.1%) [WMD = 7.97, 95% CI (5.68, 10.25)] (**Figure 10**).

FACT-G is a 27-item questionnaire assessing physical well-being, social/family well-being, emotional well-being, and functional well-being. Two studies were included in the meta-analysis on FACT-G to assess cancer-specific QOL (33, 34). The results using a random-effects model from the four subscales included physical well-being (P = 0.112, $I^2$ = 60.3%) [WMD = 1.44, 95% CI (−0.95, 3.84)]; social/family well-being (P = 0.293, $I^2$ = 9.5%) [WMD = 0.37, 95% CI (−1.39, 2.13)]; functional well-being (P = 0.628, $I^2$ = 0%) [WMD = 2.22, 95% CI (0.58, 3.86)], and emotional well-being (P = 0.388, $I^2$ = 0%) [WMD = 0.59, 95% CI (−0.70, 1.89)]. The overall change of meta-analysis showed the effect of exercise also resulted in improvements in health-related QOL (P = 0.304, $I^2$ = 16%) [WMD = 1.16, 95% CI (0.34, 1.97)] (**Figure 11**).

## 3.5 Adverse Effects

Only minor adverse events were reported, which need not medical evaluation or intervention. Three acupuncture studies have reported bruising of the skin and subcutaneous tissues,

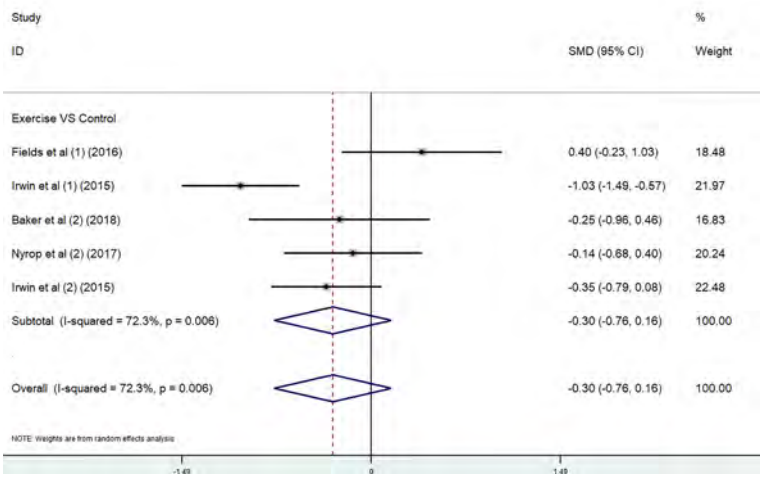



**FIGURE 6** | Overall change of exercise trials in pain, combined using (1) BPI worst pain subscale and (2) WOMAC pain subscale.

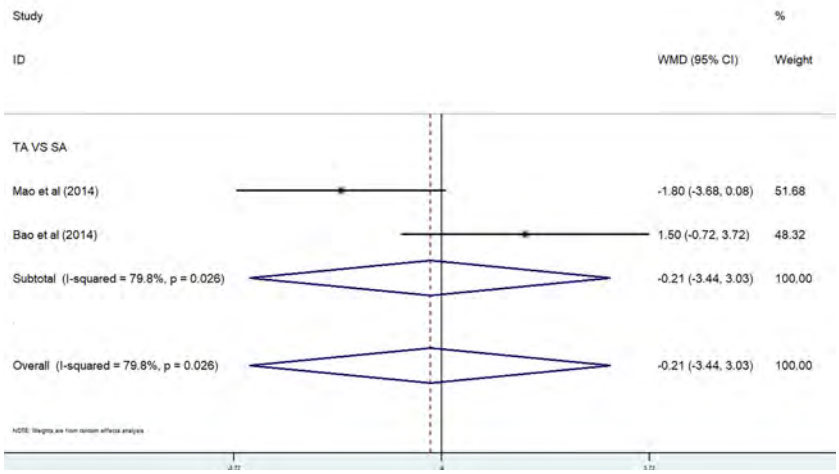



**FIGURE 7** | HADS-A subscale in acupuncture trials.

slight pain from the application of treatment to the skin, or presyncope (27, 30, 38). Three acupuncture studies reported no adverse events or no mention of adverse events (29, 37, 39). Reports of adverse events were seen in two exercise studies, such as pain, syncope, increased swelling, and extreme distress during a training session (31, 35). Four exercise studies recorded no adverse events or did not mention adverse events (32–34, 36).

## 4 DISCUSSION

This was the first systematic review and meta-analysis to evaluate the effect of PTs on psychosomatic symptoms induced by AIs in breast cancer patients. The systematic review included 11 RCTs involving 830 participants with breast cancer, and 10 studies with 798 participants were included in meta-analysis. The results show that acupuncture, compared with no treatment, could significantly improve the worst pain score, pain-related interference score, and pain severity score of the BPI scale. However, compared with no treatment, supervised exercise did not significantly improve the worst pain score of the BPI scale. The results are consistent with previous findings (21). Our results seem to suggest the superiority of acupuncture to exercise in pain improvement, though for now it is not recommended by guidelines (41, 42) and the quality of the evidence was of low level. More direct evidence that compares acupuncture and exercise therapy is needed. In addition to this, exercise was reported to result in a perceived improvement in patients'

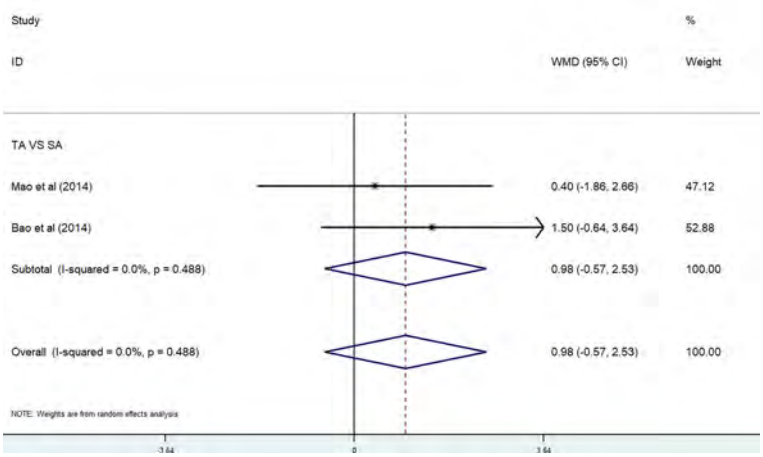



**FIGURE 8** | PSQI subscale in acupuncture trials.

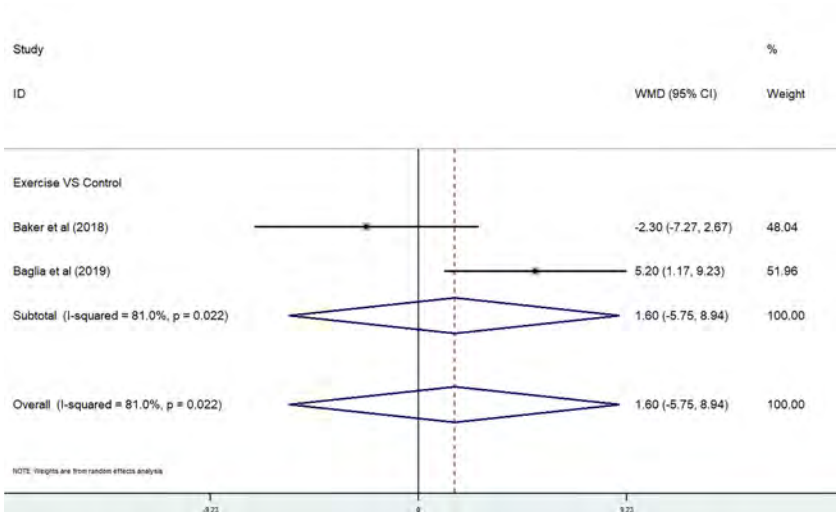



**FIGURE 9** | FACIT-Fatigue subscale in exercise trials.

QOL, suggesting its potency in enhancing patients' well-being. The evidence suggests that both acupuncture and exercise result in little to no change in anxiety, sleep disturbance, and fatigue in patients suffering from psychosomatic symptoms, but the quality of the evidence for this outcome was not high, either. Relatively, few adverse events of acupuncture and exercise were reported, which was consistent with previous findings (18, 21).

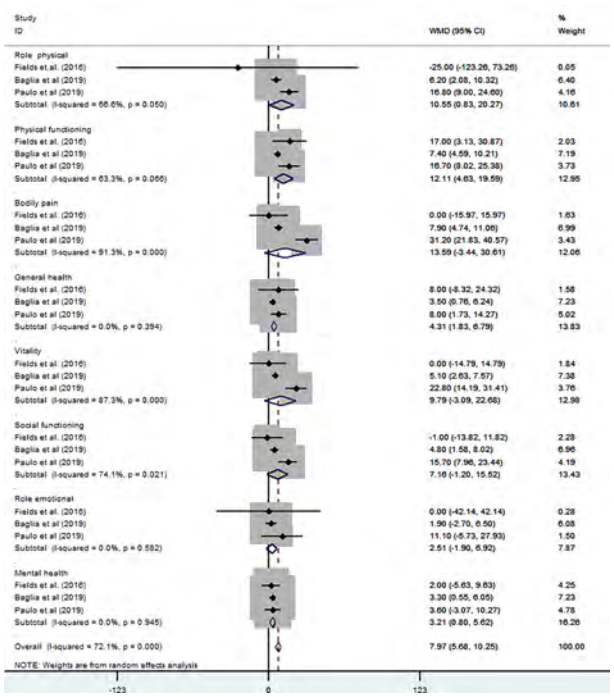



**FIGURE 10** | SF-36 subscale in exercise trials.

The worldwide use of cytotoxic chemotherapy or other antitumor means is partly encouraged by AIs antitumor efficacy and better safety profile. However, they are not free of adverse effects (43). AI-associated arthralgia (AIA) is characterized by symmetrical joint pain, mostly affecting hands, wrists, and knees, which might have significant impact on patients' QOL and compliance of treatment (44). On the individual level, breast cancer could induce anxiety and depression, as patients cannot help but worry about their future. Pain might aggravate this process, although very little is known about the pathophysiology of AIA (44). Various researches have shown significant association between perceived stress caused by pain and psychosomatic complaints (45). The definition of pain states that it is a subjective sensory and emotional experience. Pain has always been an unpleasant sensation, which has to do with both our psychosomatic conditions and previous experience of pain (46) (**Figure 12**). The notably improved clinical outcomes in breast cancer juxtaposed with significant treatment-related morbidity and mortality has led to interest in the development of de-escalated therapeutic strategies with the goal of maintaining or further improving oncologic outcomes while reducing short- and long-term toxicity and treatment-related distress (47). Currently explored strategies include replacing, reducing, or omitting cytotoxic chemotherapy; reducing dose or volume of radiotherapy; incorporation of less-invasive surgical approaches; and adjuvant therapies (48). Several clinical trials have provided treatments for AIA, among which are alternative approaches, such as physical exercise, herbal remedies, acupuncture, and yoga, though most evidence are of low quality. Presently, there were no standard, uniformly accepted treatments for AIA, and the majority of the proposed algorithms were based on anecdotal reports or derived from experiences in other pathologies, rather than from specific trials (49). This study applies more quality evidence to prove acupuncture was

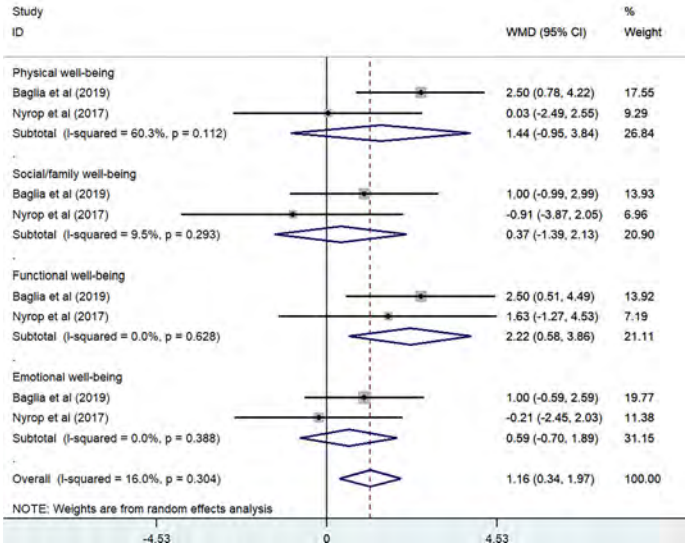



**FIGURE 11** | FACT-G subscale in exercise trials.

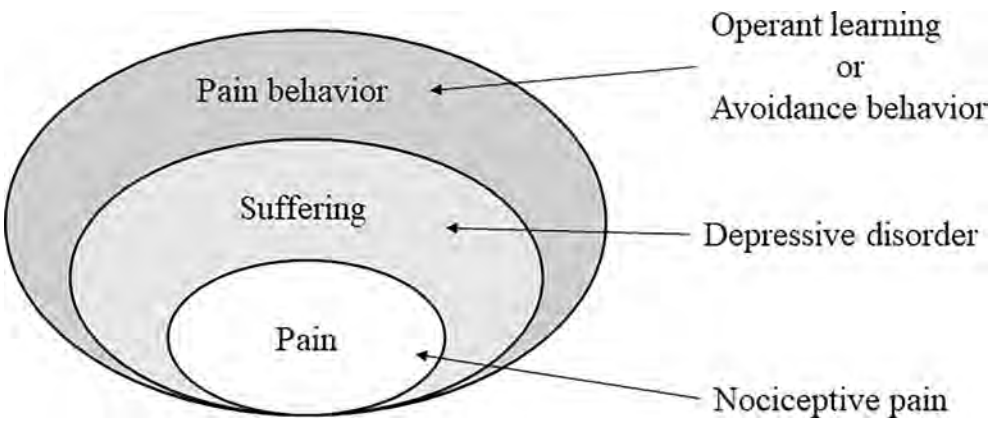



**FIGURE 12** | The chronic pain of multiaxial hierarchical structure.

associated with significant reductions in pain intensity and exercise and might improve QOL in breast cancer patients treated with AIs. Therefore, we tried to apply more stringent inclusion of recent high-quality trials to ensure the quality of RCTs and improve the credibility of evidence. This can serve as a demonstration for future design of de-escalation studies in the patient population.

Admittedly, some guidelines recommend exercise as a part of the routine lifestyle of women with breast cancer (41, 42). Furthermore, several RCTs evaluate different exercises, such as yoga, tai-chi, swimming, walking, and Pilates, which emphasized the benefits of supervised exercise on AIA, that is, pain, stiffness, grip strength, and QOL improvements (35, 50). Previous studies had shown that exercise had positive impact and significantly improved a wide range of functional, psychological, and physiological markers in individuals regardless of the type of cancer and stages of treatment (51–53). Exercise might be associated with small decreases in pro-inflammatory markers (54). Specifically, TNF and CRP were lower after training, which may have clinical relevance as both are considered as prognostic biomarkers in cancer and produced a more optimal antitumor environment (54). And our results were well in accordance with an earlier study including seven RCTs with a total of 400 enrolled patients, but didn't provide explicit evidence in favor of the benefits of supervised exercise in AIA (21). Recently, acupuncture for their role in reducing pain has been increasingly appreciated. As sham acupuncture helps avoid bias in assessing the specific outcome of acupuncture, multiple

researches and reviews had found the potential efficacy of acupuncture in reducing AIA (15, 18, 55). Available evidence has confirmed acupuncture as a key component of pain management. Furthermore, the present meta-analysis found acupuncture to be associated with demonstrable pain reduction compared to exercise and no treatment, which might show superiority of acupuncture over exercise in pain alleviation. However, few trials evaluated the influence between acupuncture and exercise. Thus, further research is needed to investigate the superiority of acupuncture to exercise in alleviating AIA.

The effect of acupuncture on life quality of patients with breast cancer treated with AIs was investigated in few studies. We only evaluated the effect of exercise on QOL in women with AIMSS. The wide range of symptomatology of AIMSS and the potential severity of symptoms could affect multiple facets of health and well-being for women (56). The results of health-related QOL and cancer-specific QOL, which was assessed using the SF-36 and FACT-G, respectively, showed that exercise training led to a moderate improvement in QOL. Nonetheless, substantial heterogeneity lowered the grade of evidence from high to moderate. Several potential mechanisms might interpret the benefits of exercise in cancer patients. First, exercise helps promote body composition and psychological benefits through maintaining cardiovascular function and metabolic parameters (57). Second, exercise elevates emotional experiences by the neural factors and neurotransmitter systems, such as the endocannabinoid system (58). Third, exercise also enhances immune function and decreases inflammatory factors, which are the possible causes of carcinogenesis (59, 60).

## 5 LIMITATIONS

Several limitations were observed and lowered the evidence grade from high to moderate. First, substantial heterogeneity damaged the credibility of the evidence, which prevented us from drawing a high-quality conclusion, although sensitivity analyses were attempted through subgroup analyses. Second, the limited number of trials included for each comparison in the meta-analysis caused unfeasibility of funnel plots, which could not fully evaluate publication bias. Third, both real acupuncture and sham acupuncture can improve pain scores, which means that sham acupuncture may provide a therapeutic benefit. The mechanism may be triggering the release of endorphins or activating pain-related neural matrix (15). Fourth, it is hardly possible to blind the participants in certain studies, such as the treatment arms in the exercise groups. Fifth, several acupuncture trials did not successfully blind their treatment arms. This may have resulted in a bias from positive patient expectations. Finally, baseline analgesic use was not specified. Consequently, variations in analgesic type and dose among participants within each study and between studies are also likely to contribute to heterogeneity.

## 6 CONCLUSIONS

Out findings show that based on moderate-level evidence, acupuncture can significantly reduce pain intensity and exercise may improve QOL in breast cancer patients treated with AIs. However, acupuncture or exercise training could not significantly improve some psychosomatic symptoms (such as anxiety, sleep disturbance, and fatigue).

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

Study conception and design: X-YZ, ZL, CC, and PZ. Acquisition, analysis, and/or interpretation of data: R-LF, B-RC, R-YL, R-TW, LX, YW, and XT. Final approval and overall responsibility for this published work: PZ and ZL. All authors contributed to the article and approved the submitted version.

## FUNDING

This work was supported by the 2020 Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine Science and Technology Innovation Special Fund (DZMKJCX-2020-027).

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.745280/full#supplementary-material

## REFERENCES

1. Koual M, Tomkiewicz C, Cano-Sancho G, Antignac JP, Bats AS, Coumoul X. Environmental Chemicals, Breast Cancer Progression and Drug Resistance. *Environ Health* (2020) 19(1):117. doi: 10.1186/s12940-020-00670-2
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2018) 68 (6):394–424. doi: 10.3322/caac.21492
3. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer Statistics in China, 2015. *CA Cancer J Clin* (2016) 66(2):115–32. doi: 10.3322/caac.21338
4. Zhang X, Li Y, Liu D. Effects of Exercise on the Quality of Life in Breast Cancer Patients: A Systematic Review of Randomized Controlled Trials. *Supportive Care Cancer* (2019) 27(1):9–21. doi: 10.1007/s00520-018-4363-2
5. Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical

Practice Guideline Focused Update. *J Clin Oncol* (2014) 32(21):2255–69. doi: 10.1200/jco.2013.54.2258
6. Nadji M, Gomez-Fernandez C, Ganjei-Azar P, Morales AR. Immunohistochemistry of Estrogen and Progesterone Receptors Reconsidered: Experience With 5,993 Breast Cancers. *Am J Clin Pathol* (2005) 123(1):21–7. doi: 10.1309/4wv79n2ghj3x1841
7. Gentry AL, Erickson KI, Sereika SM, Casillo FE, Crisafio ME, Donahue PT, et al. Protocol for Exercise Program in Cancer and Cognition (EPICC): A Randomized Controlled Trial of the Effects of Aerobic Exercise on Cognitive Function in Postmenopausal Women With Breast Cancer Receiving Aromatase Inhibitor Therapy. *Contemp Clin Trials* (2018) 67:109–15. doi: 10.1016/j.cct.2018.02.012
8. Beckwée D, Leysen L, Meuwis K, Adriaenssens N. Prevalence of Aromatase Inhibitor-Induced Arthralgia in Breast Cancer: A Systematic Review and Meta-Analysis. *Support Care Cancer* (2017) 25(5):1673–86. doi: 10.1007/s00520-017-3613-z
9. Kemp-Casey A, Roughead EE, Saunders C, Boyle F, Bulsara M, Preen DB. Switching Between Endocrine Therapies for Primary Breast Cancer: Frequency and Timing in Australian Clinical Practice. *Asia Pac J Clin Oncol* (2017) 13(2):e161–70. doi: 10.1111/ajco.12600
10. Chou R, Qaseem A, Snow V, Casey D, Cross JT Jr, Shekelle P, et al. Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline From the American College of Physicians and the American Pain Society. *Ann Intern Med* (2007) 147(7):478–91. doi: 10.7326/0003-4819-147-7-200710020-00006
11. Basbaum AI, Fields HL. Endogenous Pain Control Mechanisms: Review and Hypothesis. *Ann Neurol* (1978) 4(5):451–62. doi: 10.1002/ana.410040511
12. Chavooshi B, Saberi M, Tavallaie SA, Sahraei H. Psychotherapy for Medically Unexplained Pain: A Randomized Clinical Trial Comparing Intensive Short-Term Dynamic Psychotherapy and Cognitive-Behavior Therapy. *Psychosomatics* (2017) 58(5):506–18. doi: 10.1016/j.psym.2017.01.003
13. Weis JB, Gschwendtner K, Giesler JM, Adams L, Wirtz MA. Psychoeducational Group Intervention for Breast Cancer Survivors: A Non-Randomized Multi-Center Pilot Study. *Support Care Cancer* (2020) 28 (7):3033–40. doi: 10.1007/s00520-019-05076-6
14. Mehnert A, Brähler E, Faller H, Härter M, Keller M, Schulz H, et al. Four-Week Prevalence of Mental Disorders in Patients With Cancer Across Major Tumor Entities. *J Clin Oncol* (2014) 32(31):3540–6. doi: 10.1200/jco.2014.56.0086
15. Chien TJ, Liu CY, Chang YF, Fang CJ, Hsu CH. Acupuncture for Treating Aromatase Inhibitor-Related Arthralgia in Breast Cancer: A Systematic Review and Meta-Analysis. *J Altern Complement Med* (2015) 21(5):251–60. doi: 10.1089/acm.2014.0083
16. Mandelblatt JS, Hurria A, McDonald BC, Saykin AJ, Stern RA, VanMeter JW, et al. Cognitive Effects of Cancer and Its Treatments at the Intersection of Aging: What Do We Know; What Do We Need to Know? *Semin Oncol* (2013) 40(6):709–25. doi: 10.1053/j.seminoncol.2013.09.006
17. Faller H, Schuler M, Richard M, Heckl U, Weis J, Küffner R. Effects of Psycho-Oncologic Interventions on Emotional Distress and Quality of Life in Adult Patients With Cancer: Systematic Review and Meta-Analysis. *J Clin Oncol* (2013) 31(6):782–93. doi: 10.1200/jco.2011.40.8922
18. Liu X, Lu J, Wang G, Chen X, Xv H, Huang J, et al. Acupuncture for Arthralgia Induced by Aromatase Inhibitors in Patients With Breast Cancer: A Systematic Review and Meta-Analysis. *Integr Cancer Ther* (2021) 20:1534735420980811. doi: 10.1177/1534735420980811
19. Invernizzi M, de Sire A, Lippi L, Venetis K, Sajjad E, Gimigliano F, et al. Impact of Rehabilitation on Breast Cancer Related Fatigue: A Pilot Study. *Front Oncol* (2020) 10:556718. doi: 10.3389/fonc.2020.556718
20. Olsson Möller U, Beck I, Rydén L, Malmström M. A Comprehensive Approach to Rehabilitation Interventions Following Breast Cancer Treatment - A Systematic Review of Systematic Reviews. *BMC Cancer* (2019) 19(1):472. doi: 10.1186/s12885-019-5648-7
21. Roberts KE, Rickett K, Feng S, Vagenas D, Woodward NE. Exercise Therapies for Preventing or Treating Aromatase Inhibitor-Induced Musculoskeletal Symptoms in Early Breast Cancer. *Cochrane Database Syst Rev* (2020) 1(1): Cd012988. doi: 10.1002/14651858.CD012988.pub2
22. Xiao L-J, Tao R. "Physical Therapy". In: X Zhang, J Shi, R Tao, editors. *Substance and Non-Substance Addiction*. Singapore: Springer (2017). p. 247–60.
23. Roberts K, Rickett K, Greer R, Woodward N. Management of Aromatase Inhibitor Induced Musculoskeletal Symptoms in Postmenopausal Early Breast Cancer: A Systematic Review and Meta-Analysis. *Crit Rev Oncol Hematol* (2017) 111:66–80. doi: 10.1016/j.critrevonc.2017.01.010
24. Hershman DL, Shao T, Kushi LH, Buono D, Tsai WY, Fehrenbacher L, et al. Early Discontinuation and Non-Adherence to Adjuvant Hormonal Therapy Are Associated With Increased Mortality in Women With Breast Cancer. *Breast Cancer Res Treat* (2011) 126(2):529–37. doi: 10.1007/s10549-010-1132-4
25. Gradishar W, Salerno KE. NCCN Guidelines Update: Breast Cancer. *J Natl Compr Canc Netw* (2016) 14(5 Suppl):641–4. doi: 10.6004/jnccn.2016.0181
26. Caspersen CJ, Powell KE, Christenson GM. Physical Activity, Exercise, and Physical Fitness: Definitions and Distinctions for Health-Related Research. *Public Health Rep* (1985) 100(2):126–31.
27. Mao JJ, Farrar JT, Bruner D, Zee J, Bowman M, Seluzicki C, et al. Electroacupuncture for Fatigue, Sleep, and Psychological Distress in Breast Cancer Patients With Aromatase Inhibitor-Related Arthralgia: A Randomized Trial. *Cancer* (2014) 120(23):3744–51. doi: 10.1002/cncr.28917
28. Mao JJ, Xie SX, Farrar JT, Stricker CT, Bowman MA, Bruner D, et al. A Randomised Trial of Electro-Acupuncture for Arthralgia Related to Aromatase Inhibitor Use. *Eur J Cancer* (2014) 50(2):267–76. doi: 10.1016/j.ejca.2013.09.022
29. Bao T, Cai L, Snyder C, Betts K, Tarpinian K, Gould J, et al. Patient-Reported Outcomes in Women With Breast Cancer Enrolled in a Dual-Center, Double-Blind, Randomized Controlled Trial Assessing the Effect of Acupuncture in Reducing Aromatase Inhibitor-Induced Musculoskeletal Symptoms. *Cancer* (2014) 120(3):381–9. doi: 10.1002/cncr.28352
30. Hershman DL, Unger JM, Greenlee H, Capodice JL, Lew DL, Darke AK, et al. Effect of Acupuncture vs Sham Acupuncture or Waitlist Control on Joint Pain Related to Aromatase Inhibitors Among Women With Early-Stage Breast Cancer: A Randomized Clinical Trial. *JAMA* (2018) 320(2):167–76. doi: 10.1001/jama.2018.8907
31. Baker MK, Peddle-McIntyre CJ, Galvão DA, Hunt C, Spry N, Newton RU. Whole Body Vibration Exposure on Markers of Bone Turnover, Body Composition, and Physical Functioning in Breast Cancer Patients Receiving Aromatase Inhibitor Therapy: A Randomized Controlled Trial. *Integr Cancer Ther* (2018) 17(3):968–78. doi: 10.1177/1534735418781489
32. Paulo TRS, Rossi FE, Viezel J, Tosello GT, Seidinger SC, Simões RR, et al. The Impact of an Exercise Program on Quality of Life in Older Breast Cancer Survivors Undergoing Aromatase Inhibitor Therapy: A Randomized Controlled Trial. *Health Qual Life Outcomes* (2019) 17(1):17. doi: 10.1186/s12955-019-1090-4
33. Baglia ML, Lin IH, Cartmel B, Sanft T, Ligibel J, Hershman DL, et al. Endocrine-Related Quality of Life in a Randomized Trial of Exercise on Aromatase Inhibitor-Induced Arthralgias in Breast Cancer Survivors. *Cancer* (2019) 125(13):2262–71. doi: 10.1002/cncr.32051
34. Nyrop KA, Callahan LF, Cleveland RJ, Arbeeva LL, Hackney BS, Muss HB. Randomized Controlled Trial of a Home-Based Walking Program to Reduce Moderate to Severe Aromatase Inhibitor-Associated Arthralgia in Breast Cancer Survivors. *Oncologist* (2017) 22(10):1238–49. doi: 10.1634/theoncologist.2017-0174
35. Fields J, Richardson A, Hopkinson J, Fenlon D. Nordic Walking as an Exercise Intervention to Reduce Pain in Women With Aromatase Inhibitor–Associated Arthralgia: A Feasibility Study. *J Pain Symptom Manage* (2016) 52(4):548–59. doi: 10.1016/j.jpainsymman.2016.03.010
36. Irwin ML, Cartmel B, Gross CP, Ercolano E, Li F, Yao X, et al. Randomized Exercise Trial of Aromatase Inhibitor-Induced Arthralgia in Breast Cancer Survivors. *J Clin Oncol* (2015) 33(10):1104–11. doi: 10.1200/jco.2014.57.1547
37. Crew KD, Capodice JL, Greenlee H, Brafman L, Fuentes D, Awad D, et al. Randomized, Blinded, Sham-Controlled Trial of Acupuncture for the Management of Aromatase Inhibitor–Associated Joint Symptoms in Women With Early-Stage Breast Cancer. *J Clin Oncol* (2010) 28(7):1154–60. doi: 10.1200/jco.2009.23.4708
38. Oh B, Kimble B, Costa DS, Davis E, McLean A, Orme K, et al. Acupuncture for Treatment of Arthralgia Secondary to Aromatase Inhibitor Therapy in Women With Early Breast Cancer: Pilot Study. *Acupunct Med* (2013) 31 (3):264–71. doi: 10.1136/acupmed-2012-010309

39. Bao T, Cai L, Giles JT, Gould J, Tarpinian K, Betts K, et al. A Dual-Center Randomized Controlled Double Blind Trial Assessing the Effect of Acupuncture in Reducing Musculoskeletal Symptoms in Breast Cancer Patients Taking Aromatase Inhibitors. *Breast Cancer Res Treat* (2013) 138 (1):167–74. doi: 10.1007/s10549-013-2427-z
40. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* (2009) 6(7):e1000097. doi: 10.1371/journal.pmed.1000097
41. Newton RU, Taaffe DR, Galvao DA. Clinical Oncology Society of Australia Position Statement on Exercise in Cancer Care. *Med J Aust* (2019) 210(1):54–54.e1. doi: 10.5694/mja2.12043
42. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise Guidelines for Cancer Survivors: Consensus Statement From International Multidisciplinary Roundtable. *Med Sci Sports Exerc* (2019) 51(11):2375–90. doi: 10.1249/mss.0000000000002116
43. Hershman DL, Loprinzi C, Schneider BP. Symptoms: Aromatase Inhibitor Induced Arthralgias. *Adv Exp Med Biol* (2015) 862:89–100. doi: 10.1007/978-3-319-16366-6_7
44. Tenti S, Correale P, Cheleschi S, Fioravanti A, Pirtoli L. Aromatase Inhibitors-Induced Musculoskeletal Disorders: Current Knowledge on Clinical and Molecular Aspects. *Int J Mol Sci* (2020) 21(16). doi: 10.3390/ijms21165625
45. Zidkova R, Malinakova K, van Dijk JP, Tavel P. The Coronavirus Pandemic and the Occurrence of Psychosomatic Symptoms: Are They Related? *Int J Environ Res Public Health* (2021) 18(7). doi: 10.3390/ijerph18073570
46. Swieboda P, Filip R, Prystupa A, Drozd M. Assessment of Pain: Types, Mechanism and Treatment. *Ann Agric Environ Med* (2013) Spec no. 1:2–7.
47. Foldi J, Rozenblit M, Park TS, Knowlton CA, Golshan M, Moran M, et al. Optimal Management for Residual Disease Following Neoadjuvant Systemic Therapy. *Curr Treat Options Oncol* (2021) 22(9):79. doi: 10.1007/s11864-021-00879-4
48. Miglietta F, Dieci MV, Griguolo G, Guarneri V. Neoadjuvant Approach as a Platform for Treatment Personalization: Focus on HER2-Positive and Triple-Negative Breast Cancer. *Cancer Treat Rev* (2021) 98:102222. doi: 10.1016/j.ctrv.2021.102222
49. Nahm N, Mee S, Marx G. Efficacy of Management Strategies for Aromatase Inhibitor-Induced Arthralgia in Breast Cancer Patients: A Systematic Review. *Asia Pac J Clin Oncol* (2018) 14(6):374–82. doi: 10.1111/ajco.12845
50. Lu G, Zheng J, Zhang L. The Effect of Exercise on Aromatase Inhibitor-Induced Musculoskeletal Symptoms in Breast Cancer Survivors:a Systematic Review and Meta-Analysis. *Support Care Cancer* (2020) 28(4):1587–96. doi: 10.1007/s00520-019-05186-1
51. Stout NL, Baima J, Swisher AK, Winters-Stone KM, Welsh J. A Systematic Review of Exercise Systematic Reviews in the Cancer Literature (2005-2017). *Pm R* (2017) 9(9s2):S347–s384. doi: 10.1016/j.pmrj.2017.07.074
52. Invernizzi M, de Sire A, Venetis K, Cigna E, Carda S, Borg M, et al. Quality of Life Interventions in Breast Cancer Survivors: State of the Art in Targeted Rehabilitation Strategies. *Anticancer Agents Med Chem* (2021) 8. doi: 10.2174/1871520621666210609095602
53. Boing L, Vieira MCS, Moratelli J, Bergmann A, Guimarães ACA. Effects of Exercise on Physical Outcomes of Breast Cancer Survivors Receiving Hormone Therapy - A Systematic Review and Meta-Analysis. *Maturitas* (2020) 141:71–81. doi: 10.1016/j.maturitas.2020.06.022
54. Khosravi N, Stoner L, Farajivafa V, Hanson ED. Exercise Training, Circulating Cytokine Levels and Immune Function in Cancer Survivors: A Meta-Analysis. *Brain Behavior Immun* (2019) 81:92–104. doi: 10.1016/j.bbi.2019.08.187
55. He Y, Guo X, May BH, Zhang AL, Liu Y, Lu C, et al. Clinical Evidence for Association of Acupuncture and Acupressure With Improved Cancer Pain: A Systematic Review and Meta-Analysis. *JAMA Oncol* (2020) 6(2):271–8. doi: 10.1001/jamaoncol.2019.5233
56. Brown JC, Mao JJ, Stricker C, Hwang WT, Tan KS, Schmitz KH. Aromatase Inhibitor Associated Musculoskeletal Symptoms Are Associated With Reduced Physical Activity Among Breast Cancer Survivors. *Breast J* (2014) 20(1):22–8. doi: 10.1111/tbj.12202
57. Ramírez-Vélez R, Zambom-Ferraresi F, García-Hermoso A, Kievisiene J, Rauckiene-Michealsson A, Agostinis-Sobrinho C. Evidence-Based Exercise Recommendations to Improve Mental Wellbeing in Women With Breast Cancer During Active Treatment: A Systematic Review and Meta-Analysis. *Cancers (Basel)* (2021) 13(2). doi: 10.3390/cancers13020264
58. Saanijoki T, Tuominen L, Tuulari JJ, Nummenmaa L, Arponen E, Kalliokoski K, et al. Opioid Release After High-Intensity Interval Training in Healthy Human Subjects. *Neuropsychopharmacology* (2018) 43(2):246–54. doi: 10.1038/npp.2017.148
59. Schmidt T, van Mackelenbergh M, Wesch D, Mundhenke C. Physical Activity Influences the Immune System of Breast Cancer Patients. *J Cancer Res Ther* (2017) 13(3):392–8. doi: 10.4103/0973-1482.150356
60. Meneses-Echávez JF, Correa-Bautista JE, González-Jiménez E, Río-Valle JS, Elkins MR, Lobelo F, et al. The Effect of Exercise Training on Mediators of Inflammation in Breast Cancer Survivors: A Systematic Review With Meta-Analysis. *Cancer Epidemiol Biomarkers Prev* (2016) 25(7):1009–17. doi: 10.1158/1055-9965.Epi-15-1061


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Oncology

STUDY PROTOCOL
published: 13 December 2021
doi: 10.3389/fonc.2021.744609

# Adapted Physical Activity for Breast Cancer Patients Treated with Neoadjuvant Chemotherapy and Trastuzumab Against HER2 (APACAN2): A Protocol for a Feasibility Study

*Angeline Ginzac*[1,2*], *Maureen Bernadach*[3,4], *Ioana Molnar*[1,2], *Martine Duclos*[5], *Emilie Thivat*[1,2] *and Xavier Durando*[1,4]

[1] INSERM U1240 IMoST, Université Clermont Auvergne, Clermont-Ferrand, France, [2] Département de Recherche Clinique, Délégation Recherche Clinique et Innovation, Centre Jean PERRIN, Clermont-Ferrand, France, [3] Centre d'Investigation Clinique UMR501, Clermont-Ferrand, France, [4] Service d'Oncologie Médicale, Centre Jean PERRIN, Clermont-Ferrand, France, [5] CHU Clermont-Ferrand, Service de Médecine du Sport et des Explorations Fonctionnelles, Université Clermont Auvergne, INRAE, UNH, Clermont–Ferrand, France

OPEN ACCESS

**Edited by:**
Julio de la Torre,
Comillas Pontifical University, Spain

**Reviewed by:**
Marija Ban,
University Hospital Split, Croatia
Francesco Pepe,
University of Naples Federico II, Italy
Marco Invernizzi,
University of Eastern Piedmont, Italy

***Correspondence:**
Angeline Ginzac
angeline.ginzac@clermont.unicancer.fr

**Specialty section:**
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

**Received:** 20 July 2021
**Accepted:** 24 November 2021
**Published:** 13 December 2021

**Citation:**
Ginzac A, Bernadach M, Molnar I, Duclos M, Thivat E and Durando X (2021) Adapted Physical Activity for Breast Cancer Patients Treated with Neoadjuvant Chemotherapy and Trastuzumab Against HER2 (APACAN2): A Protocol for a Feasibility Study. Front. Oncol. 11:744609. doi: 10.3389/fonc.2021.744609

**Background:** The standard care for HER2-positive breast cancer is chemotherapy plus a HER2-directed therapy. This can lead to treatment-induced cardiotoxicity. On the other hand, the practice of physical activity is known to improve cardiac function; thus HER2-positive breast cancer patients could draw particular benefit from physical activity during treatment. However, at the time of diagnosis for breast cancer, the majority of patients are insufficiently active according to physical activity recommendations of World Health Organisation, and it is difficult to remain or become active during the treatment. There is a lack of data in the literature on the optimal program to propose to patients to encourage them to be active during treatment. The aim of our study is to assess the feasibility of a home-based physical activity program during neoadjuvant chemotherapy and trastuzumab for HER2-positive breast cancer.

**Methods:** The APACAN2 study is a single-centre, non-randomized interventional trial. Patients with HER2-positive breast cancer treated with anthracycline-based neoadjuvant chemotherapy and trastuzumab are eligible for enrolment. The supervised home-based physical activity program takes place during neoadjuvant chemotherapy (NACT). It combines aerobic and strengthening exercises. The primary endpoint is the proportion of patients reaching the international physical activity recommendations, i.e. 150 minutes of moderate-intensity activity per week at the end of NACT. The study started in April 2018 and seventy patients are expected to be recruited.

**Discussion:** In the literature, the majority of studies on practice of physical activity in breast cancer focus on adjuvant chemotherapy or on the period after the end of

treatment. To the best of our knowledge, the APACAN2 study is the first to evaluate a home-based physical activity program during neoadjuvant chemotherapy for HER2-positive breast cancer.

**Trial Registration Number:** Clinicaltrials.gov: NCT02963363, registered on July 11, 2016. Identifier with the French National Agency for the Safety of Medicines and Health Products N°ID RCB 2016-A01344-47, registered in August 2016. Protocol: version 8, 24 February 2021.

**Keywords: HER2-positive breast cancer, adapted physical activity, neoadjuvant chemotherapy, HER2-directed therapy, feasibility study**

## 1 INTRODUCTION

Worldwide, breast cancer is the most commonly diagnosed cancer among women and is also the leading cause of cancer death (1). Overexpression of human epidermal growth factor receptor 2 (HER2) concerns approximately 15% of breast cancer patients. This subtype of cancer is associated with a poorer disease-free survival and overall survival (2, 3). The standard care to treat these tumours is chemotherapy plus HER2-directed therapy administered in combination with standard chemotherapy (anthracycline and taxane-based). This treatment reduces both the rate of recurrence and the mortality rate, respectively by half and by one third. However, trastuzumab (the most commonly used HER2-directed therapy) is known to be associated with cardiotoxicity (4). Anthracycline-based chemotherapy also causes cardiotoxicity (5, 6). Between 1 and 4% of patients treated with trastuzumab develop heart failure is and nearly 10% have asymptomatic LVEF reduction (7–10). It has been estimated that the cumulative incidence rate for major cardiac events (as for example pulmonary edema, cardiomyopathy; cardiovascular death) is 6.6% for sequential therapy, i.e. anthracycline and trastuzumab (11).

As a result, HER2-positive breast cancer patients are exposed to treatment-induced cardiotoxicity. This can have serious consequences, such as treatment discontinuation (12).

Physical exercise is known to improve quality of life during and after breast cancer treatment (13–16). It can also be beneficial for cardiac function. Eight weeks of aerobic practice during adjuvant chemotherapy for breast cancer have led to an increase in oxygen peak consumption reflecting an improvement in cardio-respiratory capacities (17). The longer the physical activity program, the greater the improvement in oxygen peak consumption (ranging from 0.6 ml/min/kg after 12 weeks to 1.83 ml/min/kg after 27 weeks of practice) (18–20). In addition, physical activity could protect the cardiovascular system, so that it could be a strategy to limit treatment-induced cardiotoxicity in the HER2-positive population. However, at diagnosis of breast cancer, the majority of patients have insufficient levels of physical activity and do not reach the international recommendations (21–25). These recommendations are issued by the World Health Organisation (WHO) for the healthy population, and correspond to 150 minutes of moderate-intensity activity or 75 minutes of vigorous activity or an equivalent combination of moderate and vigorous activity per week (26) and to limit time spent in sedentary behaviors. Nevertheless, it can be difficult to maintain physical activity during treatment because of several barriers relating to care, and also personal barriers (27).

Numerous interventional clinical trials have been set up to promote adapted physical activity during breast cancer treatment. The notion of adapted physical activity refers to physical activities and sports that are adapted to the capacities of people because of their health condition. The proposed programs are heterogeneous in terms of exercises (aerobic and/or muscular strengthening), duration of sessions, duration of the program (a few weeks to several months), intensity or even the mode of practice (alone or in a group, supervised or not) (27).

In the literature data, there are few trials exploring the interest in physical activity for the HER2-positive breast cancer subpopulation. Haykowski's study (aerobic exercise, three sessions of 30 to 60 minutes/week) concerned the first four months of trastuzumab administration and did not evidence any improvement in cardiac function (28). On the contrary, left ventricular cavity dilation and significant decreases in the ventricular ejection fraction were observed. The authors pointed out that the poor adherence to exercise sessions could explain this result, because cardiopulmonary function improved for patients that completed ≥ 55% of the sessions. A randomized controlled study among HER2-positive patients showed that patients who followed the aerobic intervention during their neoadjuvant chemotherapy (3 sessions per week, one-to-one supervised sessions) improved their cardiopulmonary function while it decreased in the control group patients (29). In France, the CARDAPAC phase II study conducted on HER2-positive patients treated with trastuzumab alone has just been completed (30). The aim was to assess the impact of 3 months' aerobic exercise on cardiac function and on the incidence of cardiotoxicity. The program started at the end of chemotherapy and consisted in 3 sessions of 45 minutes a week.

The practice of physical activity is recommended as soon as possible at the beginning of treatment for breast cancer patients (31–33). However, in the literature, the majority of the programs

**Abbreviations:** APA, Adapted physical activity; CI, confidence interval; HDL, High density lipoprotein; HER2, Human epidermal growth factor receptor 2; LDL, Low density lipoprotein; LVEF, Left ventricular ejection fraction; MFI-20, Multidimensional fatigue inventory; MSE, Medico-sports educator; NACT, Neoadjuvant chemotherapy; QLQ-C30, Quality of life questionnaire core 30; QOL; Quality of life; RPAQ, Recent physical activity questionnaire.

are offered in the course of adjuvant chemotherapy or in the post-treatment period. Furthermore, there is a lack of information in the literature about the interest of physical activity practice for HER2-positive breast cancer patients. In this context, Jean PERRIN Centre has initiated a prospective interventional study in order to study the feasibility of a home-based physical activity intervention among HER2-positive breast cancer patients currently treated with neoadjuvant chemotherapy + targeted therapy. The objective of the intervention is to achieve or maintain a physical activity level corresponding to the WHO international recommendations at the end of chemotherapy and to limit time spent in sedentary behaviors.

# 2 METHODS AND ANALYSIS

## 2.1 Study Design

APACAN2 is a French single-centre, prospective, interventional, non-randomized trial designed to assess the feasibility of a home-based adapted physical activity (APA) intervention during neoadjuvant chemotherapy for early HER2-positive breast cancer (NCT02963363).

Seventy patients are expected to be recruited. Patient enrolment is expected to take 6 years and the study duration for each patient is 20 months.

Participants can withdraw at any time. Data obtained will be retained with consent, and any reasons given for withdrawal will be recorded.

## 2.2 Coordination

The Centre Jean PERRIN is the sponsor and is responsible for coordination, trial management, data management and trial monitoring.

## 2.3 Study Objectives and Endpoints

### 2.3.1 Primary Objective and Endpoint

The primary objective of the APACAN2 trial is to demonstrate the feasibility of a home-based adapted physical activity (APA) program for patients with HER2 positive breast cancer receiving neoadjuvant chemotherapy. Therefore, the primary endpoint is the proportion of patients reaching the international recommendations for physical activity at the end of chemotherapy. It will be evaluated using the recent physical activity questionnaire (RPAQ) which will be completed before and at the end of neoadjuvant chemotherapy (34).

### 2.3.2 Secondary Objectives and Endpoints

The secondary objectives of the APACAN 2 trial are:

- assessment of the impact of the APA program on exercising time and sedentary time; quality of life; fatigue; weight; physical capacities; physical activity in the rest of the day; lipid profile; ventricular ejection fraction. This will be evaluated using questionnaires [RPAQ (34), QLQ-C30 (35), MFI-20 (36)], physical tests, blood tests and cardiac ultrasound. This data will be collected at baseline, at the end of chemotherapy and at the beginning and the end of targeted therapy.
- description of the longitudinal evolution of physical activity and sedentary behaviour at each step of treatment,
- exploration of barriers to program uptake,
- conditions of the return to work,
- exploration of changes in cancer treatment.

## 2.4 Study Procedures and Participant Timeline

An overview of the study assessments and procedures is presented in **Table 1**.

Four visits are follow-up appointments for each enrolled patients: inclusion [before the beginning of neoadjuvant chemotherapy (NACT)], at the end of NACT, at the beginning and at the end of HER2-targeted therapy. The study layout is presented in **Figure 1**.

## 2.5 Measures at Each of the Four Assessments

### 2.5.1 Physical Activity and Sedentariness

The assessment of physical activity and sedentariness will be performed using the modified RPAQ. This questionnaire covers four areas of activity: domestic activities, leisure activities, professional activities, and modes of travel. This questionnaire provides information on the time spent on different activities in each of the four areas mentioned above. Specific energy expenditure is associated with each physical activity, which makes it possible to estimate the overall energy expenditure of patients using Ainsworth compendium (37). It also provides information on the time spent sedentary (work, leisure, travel).

### 2.5.2 Measurement of Muscle Strength and Muscular Endurance

An isokinetic dynamometer will be used to measure the maximum knee extension torque. Subjects will perform the movement with their non-dominant leg (which will be determined as the leg not used to kick a ball). Measurements will be made at different speeds (30, 60 and 120°/s). For each speed, two trials of 3 successive repetitions will be performed and the best performance will be kept as the maximum isokinetic torque at a given speed. The subjects will have 2 minutes of rest between each trial. Finally, the maximum isometric knee extension torque will be measured at a 120° angle. Subjects will perform a maximal contraction over 5 seconds or until the isometric torque trace peaks. Subjects will be given 3 trials and 3 minutes of rest between each trial. The best trial will be considered the maximum isometric knee extension torque.

For the upper limbs, muscular strength will be measured with both right and left arm using a dynamometer (hand grip Takei TK 200). Measures will be repeated three times and the best score for each side is retained.

To measure muscular endurance of the lower limbs, the objective for the patient is to maintain a level of force corresponding to 75% of her maximum voluntary force for as long as possible.

**TABLE 1** | Study timeline.

| | Inclusion (before NACT) | Standard evaluation during NACT | End of NACT +/- trastuzumab | First administration of adjuvant trastuzumab | Last administration of adjuvant trastuzumab |
|---|---|---|---|---|---|
| | | APA intervention | | | |
| Consent | ✓ | | | | |
| Clinical examination | ✓ | ✓ | ✓ | ✓ | ✓ |
| Previous and ongoing treatments | ✓ | ✓ | ✓ | ✓ | ✓ |
| Toxicities assessment | ✓ | ✓ | ✓ | ✓ | ✓ |
| Follow-up of cancer treatment (adaptation, delay, termination) | | ✓ | ✓ | ✓ | ✓ |
| Anthropometric measures | ✓ | ✓ | ✓ | ✓ | ✓ |
| Physical capacities evaluation | | | | | |
| Measurement of cardiorespiratory aerobic capacity | ✓ | | | | ✓ |
| Measurement of muscle strength and muscular endurance | ✓ | | ✓ | ✓ | ✓ |
| Physical activity and sedentarity (modified RPAQ) | ✓ | | ✓ | ✓ | ✓ |
| QLQ-C30 and MFI20 questionnaire | ✓ | | ✓ | ✓ | ✓ |
| Lipid test | ✓ | | ✓ | ✓ | ✓ |
| Cardiac ultrasound | ✓ | | ✓ | ✓ | ✓ |

*APA, Adapted physical activity.*
*NACT, Neoadjuvant chemotherapy.*
*RPAQ, Recent Physical Activity Questionnaire.*
*QLQ-C30, Quality of Life Questionnaire - Core 30.*
*MFI-20, Mutidimensional Fatigue Inventory.*

### 2.5.3 Measurement of Cardiorespiratory Aerobic Capacity

This measure is not mandatory for all patients in order not to delay the beginning of treatment (not related to primary objective) and is expected to be performed twice during participation in the study: at baseline and at the end of the study.

The subjects performed a progressive cycling test on an electromagnetically braked cycle ergometer (Ergoline, Bitz, Germany) until volitional exhaustion to determine the maximal values of ventilation (VEmax), oxygen uptake (VO2max), carbon dioxide output and respiratory exchange ratio (RERmax) by direct method (Oxycon Pro, JAEGER, Germany). VO2 and VCO2 were measured breath-by-breath through a mask connected to O2 and CO analysers (Oxycon Pro-Delta, Jaeger, Hoechberg, Germany). Calibration of gases analysers was performed with commercial gases of known concentration. Ventilatory parameters were averaged every 30 s. Electrocardiogram and heart rate (HR) were measured continuously using 10 precordial electrodes. The first stage of the test lasted 3 min, and the initial power output was 35 W. Power output was then increased by 20 W every 2 min 30 s. Pedaling rate was maintained at 60 revolutions per minute. Criteria for the achievement of VO2max were subjective exhaustion the participants' maximal HR (HRmax) was closed to their age-predicted maximum HR (i.e., 220-age ± 10 beats.min-1) and/or Respiratory Exchange ratio (RER, VCO2/VO2) above 1.02 and/or a plateau of VO2.

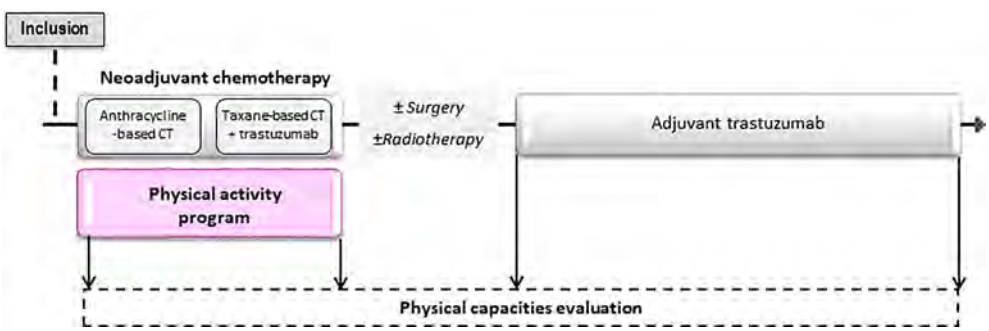



**FIGURE 1** | Design of the APACAN2 study. The APA program take place from the beginning to the end of neo-adjuvant chemotherapy. Four follow-up visits are planned during the study.

### 2.5.4 6-Minute Walking Test

The test will be run twice in order to reduce the "first time" effect. This test measures the distance a patient can walk in six minutes and thus allows the evaluation of the global and integrated responses of all systems involved during exercise and is considered a proxy for cardiorespiratory capacity. A score is obtained in meters. This test will be performed following the guidelines of the American Thoracic Society (38)and has been tested and validated in the past (39).

### 2.5.5 Self-Administered Questionnaires

The QLQ-C30 (Quality of Life Questionnaire-Core 30) and the MFI20 (Multidimensional Fatigue Inventory) will enable us to evaluate respectively the patient's quality of life (QoL) and fatigue during the study.

### 2.5.6 Anthropometric Measures

Weight will be measured to within ± 0.1 kg on the same scales. The body mass index will be calculated from this data.

Waist circumference will be measured with a tape measure.

Pulse, blood pressure and temperature will be measured by a nurse at the investigating centre.

### 2.5.7 Lipid Test

A lipid assessment will be performed at inclusion, at the end of neoadjuvant chemotherapy and on the day of the first and last administration of anti-HER2 therapy. This assessment will include the determination of total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides. These parameters give an indication of possible cardiovascular risk factors. It will require the collection of 5 ml of blood.

### 2.5.8 Cardiac Ultrasound

A cardiac ultrasound scan will be performed at each of the four appointments. The ventricular ejection fraction results will be evaluated by a cardiologist and compared in order to assess the effect of the APA program on the impact of treatments on cardiac capacity. The cardiac ultrasound is an essential measure for management of cardiovascular function. The same method will be used for each of the assessments for each patient.

## 2.6 Selection Criteria

The inclusion and non-inclusion criteria are presented in **Table 2**. Patients will be eligible for the study if they have HER2-positive breast cancer with an indication for treatment with neoadjuvant chemotherapy (anthracycline-based) and targeted therapy. They will be ineligible if they have a contraindication for physical activity, a metastatic cancer or a Karnofsky index ≤ 90%

## 2.7 Description of the APA Intervention

The intervention takes place during the neoadjuvant chemotherapy period, i.e. lasting about 18 weeks. The APA program is composed of aerobic exercises and muscle strengthening. An exercise booklet will explain to the patients the different exercises to perform.

Before the beginning of the program, the medical-sports educator (MSE) will demonstrate every exercise of the booklet to the patients. Thereafter patients will perform the program at home. The MSE will call each patient every week to review the program progress and increase or decrease the intensity of exercise according to the patient's experiences.

The aerobic exercises consist in walking on at least five days a week. The duration of walking sessions should increase every week to reach 30 minutes walking per day.

Three times a week, the patients are to perform muscle strengthening with at least 4 different exercises, to mobilize the lower and upper limbs, among those proposed in the booklet. For each of them, the patient are to perform 3 sets of 8 to 12 repetitions with 1 minute of rest between each set.

Patients are asked note all the exercise sessions they do. They should also mention any other physical activity week by week, such as hiking, gardening or cleaning.

## 2.8 Statistical Analysis

The analysis will be done by the biostatistician of clinical research department in Jean PERRIN Center.

### 2.8.1 Sample Size

Our hypothesis is that at least 65% of the patients will have reached the physical activity recommendations at the neoadjuvant

**TABLE 2** | Selection criteria.

| | |
|---|---|
| **Inclusion criteria** | - Woman 18 years old and older |
| | - Patient with HER2-positive breast cancer, histologically confirmed, eligible to a neoadjuvant chemotherapy and an anti-HER2 target therapy |
| | - Covered by social security system |
| | - Signed informed consent |
| | - Certificate of non-contraindication to the practice of physical activity |
| **Non-inclusion criteria** | - History of cancer in the last five years except basocellular |
| | - Metastatic cancer |
| | - Karnofsky index ≤ 90% |
| | - Men |
| | - Pregnant women |
| | - Patient with psychiatric or cognitive disorders |
| | - Patient deprived of liberty by judicial or administrative decision |
| | - Contraindication to the practice of physical activity |
| | - Insufficient knowledge or understanding of the French language to fill in self-questionnaires correctly or to answer an interrogation |
| | - Participation to another clinical study with a similar objective |

post-chemotherapy evaluation. A total of 70 patients is required to have an accuracy of ± 10% with a 95% confidence interval (CI). Given this CI, the trial will be considered positive if more than 75% of our population complies with the international recommendations.

### 2.8.2 Data Analysis

#### *2.8.2.1 Primary Analysis*

The primary endpoint will be the percentage of individuals with physical activity after neoadjuvant chemotherapy, as assessed by the RPAQ with 150 minutes or more per week of moderate intensity or 75 minutes or more of vigorous intensity endurance activity or an equivalent combination of moderate to vigorous activity per week. The 95% confidence interval of this percentage will be calculated using Pearson's approximation. If this confidence interval is greater than 65%, the intervention will be considered effective. Its feasibility will then be demonstrated. If it only reaches 65% but is greater than 50%, the intervention will be considered "questionable" and below this, its effectiveness will be considered nil.

#### *2.8.2.2 Secondary Analysis*

To assess the impact of the APA program, a comparative analysis of these before/after changes will be carried out on physical activity (MET-h/week), sedentariness (minutes), QoL (overall score, sub scores), fatigue, weight, physical capacities (endurance, muscular strength, flexibility), lipid balance, and cardiac function. The following common tests will be used: paired Student's t-test, Mann-Whitney U-test, and $Chi^2$ for paired series for qualitative criteria. We will also evaluate the impact of levels of physical activity and compliance with recommendations on these parameters using the following tests: ANOVA, Pearson's correlation or Spearman rank tests depending on whether the distributions are Gaussian and homoscedastic.

The effect of the physical activity levels on compliance to the program will be tested by correlations. The Hryniuk score will be used to explore the treatment changes occurring.

Concerning the resumption of professional activity, a survival curve for time to recovery will be calculated.

Concerning the analysis of the longitudinal evolution of physical activity and time spent in sedentary behaviour, a mixed-model ANOVA will be used.

The evaluation of barriers to physical activity adherence will be carried out using the following tests: ANOVA, Pearson's correlation or Spearman's rank tests depending on whether the distributions are Gaussian and homoscedastic. A logistic regression will test the respective influence of the different factors on whether or not the recommendations are met.

The secondary endpoints will be compared to control data from the Jean Perrin Centre or with data from the literature whenever possible.

The standard significance level ($p < 0.05$) will be used for these analyses. As this trial is exploratory, no correction for multiple comparisons will be made.

## 2.9 Data Management And Monitoring

The data collected for the trial will be entered on an electronic case report form (eCRF) (EnnovClinical). The people with access to the data will be the investigators, the clinical research associates, the project leader and the biostatistician. They are authorized professionals and are subject to professional secrecy. The investigator will ensure the accuracy, completeness, and reliability of the data recorded (pseudonymized patient data) and the provision of answers to data queries.

Regular monitoring will be carried out by a clinical research associate mandated by the sponsor. The objectives will be to ensure the correct conduct of the study in each centre, the collection and recording of data generated in writing, its documentation, recording and reporting, in accordance with the legislative and regulatory provisions in force. Monitoring reports will ensure traceability.

## 2.10 Trial Status

The APACAN2 trial is currently recruiting. Participant recruitment began in April 2018 and is expected to finish in December 2022. The approved protocol is version 8, dated 24/02/2021.

# 3 DISCUSSION

The APACAN2 trial aims to assess the feasibility of a home-based adapted physical activity program during neoadjuvant chemotherapy for HER2-positive breast cancer. In to this intervention, we aim to encourage physical activity from the beginning of the treatment by proposing a physical activity program at home and without time constraints. In addition, we focus on a population that can draw particular benefit from the practice of physical activity because of the treatment-induced cardiotoxity to which HER2-positive patients are exposed.

The current standard care to monitor cardiotoxicity is left ventricular ejection fraction (LVEF) monitoring (40–42). However, this method has some limits, as it lacks sensitivity, and does not enable early detection of cardiotoxicity. New techniques are currently developing, such as the titration of troponin in the blood. This biomarker is recognized as predictive of cardiotoxicity occurrence during treatment by the Food and Drug Administration and in several studies because it precedes decreases in LVEF (43–46). It would be interesting to follow levels of biomarkers such as troponin for the patients participating in the study.

We have chosen not to use a randomized design because it is a feasibility study and it was important that as many patients as possible should benefit from the intervention. According to the APACAN2 results, we could subsequently propose a randomized study. Another limit of our study is that the anthropometric measures and lipid test are done when the patient come for her consultation so they are not always fasting.

The strength of our study is that the physical activity program is proposed at the beginning of the treatment, as recommended. In the literature, the majority of studies deploy the physical activity program in the course of adjuvant chemotherapy or later. There is little data about physical activity and sedentariness during neoadjuvant chemotherapy for breast cancer. Furthermore, the home-based concept makes it possible to take geographical and temporal constraints into account. Indeed, patients are free to organise their sessions as they wish without complying with a specific imposed calendar, and they are not obliged to travel to a given place to train.

## ETHICS STATEMENT

The study protocol and its amendments has obtained approval from the French Ethics Committee (Comité de Protection des Personnes Sud-Est VI) (N°ID RCB 2016-A01344-47) in November 2016. The study is conducted in accordance with the Helsinki Declaration, the Good Clinical Practice (GCP) guidelines of the International Conference on Harmonisation (ICH–E6, 17/07/96).

## AUTHOR CONTRIBUTIONS

AG, IM, ET and XD wrote the protocol. XD is the coordinator of the study. IM is the statistical expert, contributed to sample size calculations and developed the experimental plan. She will undertake the statistical analyses. MD supervised the physical activity evaluation. AG is the project manager of the study and is involved in aspects of the day-to-day running of the trial. She wrote the first draft of this manuscript and contributed to the grant proposal. All authors critically revised the manuscript, gave final approval of the manuscript and are accountable for the accuracy and integrity of the manuscript.

## FUNDING

This work received funding from the Quality of life Pink Ribbon Award by the association "Ruban Rose" in 2019 (www.cancerdusein.org).

## REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2018) 68:394–424. doi: 10.3322/caac.21492
2. Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, Fehrenbacher L, et al. Multinational Study of the Efficacy and Safety of Humanized Anti-HER2 Monoclonal Antibody in Women Who Have HER2-Overexpressing Metastatic Breast Cancer That has Progressed After Chemotherapy for Metastatic Disease. *J Clin Oncol* (1999) 17:2639–48. doi: 10.1200/JCO.1999.17.9.2639
3. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human Breast Cancer: Correlation of Relapse and Survival With Amplification of the HER-2/Neu Oncogene. *Science* (1987) 235:177–82. doi: 10.1126/science.3798106
4. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab Containing Regimens for Early Breast Cancer. *Cochrane Database Syst Rev* (2012) CD006243. doi: 10.1002/14651858.CD006243.pub2
5. Mantarro S, Rossi M, Bonifazi M, D'Amico R, Blandizzi C, La Vecchia C, et al. Risk of Severe Cardiotoxicity Following Treatment With Trastuzumab: A Meta-Analysis of Randomized and Cohort Studies of 29,000 Women With Breast Cancer. *Intern Emerg Med* (2016) 11:123–40. doi: 10.1007/s11739-015-1362-x
6. Chen T, Xu T, Li Y, Liang C, Chen J, Lu Y, et al. Risk of Cardiac Dysfunction With Trastuzumab in Breast Cancer Patients: A Meta-Analysis. *Cancer Treat Rev* (2011) 37:312–20. doi: 10.1016/j.ctrv.2010.09.001
7. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer That Overexpresses HER2. *N Engl J Med* (2001) 344:783–92. doi: 10.1056/NEJM200103153441101
8. Sengupta PP, Northfelt DW, Gentile F, Zamorano JL, Khandheria BK. Trastuzumab-Induced Cardiotoxicity: Heart Failure at the Crossroads. *Mayo Clin Proc* (2008) 83:197–203. doi: 10.4065/83.2.197
9. Farolfi A, Melegari E, Aquilina M, Scarpi E, Ibrahim T, Maltoni R, et al. Trastuzumab-Induced Cardiotoxicity in Early Breast Cancer Patients: A Retrospective Study of Possible Risk and Protective Factors. *Heart* (2013) 99:634–9. doi: 10.1136/heartjnl-2012-303151
10. Fried G, Regev T, Moskovitz M. Trastuzumab-Related Cardiac Events in the Treatment of Early Breast Cancer. *Breast Cancer Res Treat* (2013) 142:1–7. doi: 10.1007/s10549-013-2732-6
11. Thavendiranathan P, Abdel-Qadir H, Fischer HD, Camacho X, Amir E, Austin PC, et al. Breast Cancer Therapy-Related Cardiac Dysfunction in Adult Women Treated in Routine Clinical Practice: A Population-Based Cohort Study. *J Clin Oncol* (2016) 34:2239–46. doi: 10.1200/JCO.2015.65.1505
12. McArthur HL, Chia S. Cardiotoxicity of Trastuzumab in Clinical Practice. *N Engl J Med* (2007) 357:94–5. doi: 10.1056/NEJMc070065
13. Carayol M, Bernard P, Boiché J, Riou F, Mercier B, Cousson-Gélie F, et al. Psychological Effect of Exercise in Women With Breast Cancer Receiving Adjuvant Therapy: What is the Optimal Dose Needed? *Ann Oncol* (2013) 24:291–300. doi: 10.1093/annonc/mds342
14. Furmaniak AC, Menig M, Markes MH. Exercise for Women Receiving Adjuvant Therapy for Breast Cancer. *Cochrane Database Syst Rev* (2016) 9:CD005001. doi: 10.1002/14651858.CD005001.pub3
15. Invernizzi M, de Sire A, Venetis K, Cigna E, Carda S, Borg M, et al. Quality of Life Interventions in Breast Cancer Survivors: State of the Art in Targeted Rehabilitation Strategies. *Anticancer Agents Med Chem* (2021) 21. doi: 10.2174/1871520621666210609095602
16. Zeng Y, Huang M, Cheng ASK, Zhou Y, So WKW. Meta-Analysis of the Effects of Exercise Intervention on Quality of Life in Breast Cancer Survivors. *Breast Cancer* (2014) 21:262–74. doi: 10.1007/s12282-014-0521-7
17. Kim C-J, Kang D-H, Smith BA, Landers KA. Cardiopulmonary Responses and Adherence to Exercise in Women Newly Diagnosed With Breast Cancer Undergoing Adjuvant Therapy. *Cancer Nurs* (2006) 29:156–65. doi: 10.1097/00002820-200603000-00013
18. Cornette T, Vincent F, Mandigout S, Antonini MT, Leobon S, Labrunie A, et al. Effects of Home-Based Exercise Training on VO2 in Breast Cancer Patients Under Adjuvant or Neoadjuvant Chemotherapy (SAPA): A Randomized Controlled Trial. *Eur J Phys Rehabil Med* (2016) 52:223–32.
19. Foucaut A-M, Berthouze-Aranda SE, Touillaud M, Kempf-Lépine A-S, Baudinet C, Meyrand R, et al. Reduction of Health Risk Factors Through an Adapted Physical Activity Program in Patients With Breast Cancer. *Support Care Cancer* (2014) 22:1097–104. doi: 10.1007/s00520-013-2065-3
20. Leach HJ, Danyluk JM, Nishimura KC, Culos-Reed SN. Benefits of 24 Versus 12 Weeks of Exercise and Wellness Programming for Women Undergoing Treatment for Breast Cancer. *Support Care Cancer* (2016) 24:4597–606. doi: 10.1007/s00520-016-3302-3
21. Blanchard CM, Courneya KS, Stein K. American Cancer Society's SCS-II. Cancer Survivors' Adherence to Lifestyle Behavior Recommendations and Associations With Health-Related Quality of Life: Results From the American Cancer Society's SCS-II. *J Clin Oncol* (2008) 26:2198–204. doi: 10.1200/JCO.2007.14.6217
22. Coups EJ. Ostroff JS. A Population-Based Estimate of the Prevalence of Behavioral Risk Factors Among Adult Cancer Survivors and Noncancer Controls. *Prev Med* (2005) 40:702–11. doi: 10.1016/j.ypmed.2004.09.011
23. Eakin EG, Youlden DR, Baade PD, Lawler SP, Reeves MM, Heyworth JS, et al. Health Behaviors of Cancer Survivors: Data From an Australian Population-Based Survey. *Cancer Causes Control* (2007) 18:881–94. doi: 10.1007/s10552-007-9033-5
24. Harrison S, Hayes SC, Newman B. Level of Physical Activity and Characteristics Associated With Change Following Breast Cancer Diagnosis and Treatment. *Psychooncology* (2009) 18:387–94. doi: 10.1002/pon.1504
25. Turner RR, Steed L, Quirk H, Greasley RU, Saxton JM, Taylor SJ, et al. Interventions for Promoting Habitual Exercise in People Living With and

Beyond Cancer. *Cochrane Database Syst Rev* (2018) 9:CD010192. doi: 10.1002/14651858.CD010192.pub3
26. WHO. *Global Recommendations on Physical Activity for Health* (2010). Geneva: World Health Organization. Available at: http://www.ncbi.nlm.nih.gov/books/NBK305057/ (Accessed May 7, 2018).
27. Ginzac A, Passildas J, Gadéa E, Abrial C, Molnar I, Trésorier R, et al. Treatment-Induced Cardiotoxicity in Breast Cancer: A Review of the Interest of Practicing a Physical Activity. *Oncology* (2019) 96:223–34. doi: 10.1159/000499383
28. Haykowsky MJ, Mackey JR, Thompson RB, Jones LW, Paterson DI. Adjuvant Trastuzumab Induces Ventricular Remodeling Despite Aerobic Exercise Training. *Clin Cancer Res* (2009) 15:4963–7. doi: 10.1158/1078-0432.CCR-09-0628
29. Hornsby WE, Douglas PS, West MJ, Kenjale AA, Lane AR, Schwitzer ER, et al. Safety and Efficacy of Aerobic Training in Operable Breast Cancer Patients Receiving Neoadjuvant Chemotherapy: A Phase II Randomized Trial. *Acta Oncol* (2014) 53:65–74. doi: 10.3109/0284186X.2013.781673
30. Jacquinot Q, Meneveau N, Chatot M, Bonnetain F, Degano B, Bouhaddi M, et al. A Phase 2 Randomized Trial to Evaluate the Impact of a Supervised Exercise Program on Cardiotoxicity at 3 Months in Patients With HER2 Overexpressing Breast Cancer Undergoing Adjuvant Treatment by Trastuzumab: Design of the CARDAPAC Study. *BMC Cancer* (2017) 17:425. doi: 10.1186/s12885-017-3420-4
31. Foucaut A-M, Berthouze SE, Touillaud M, Morelle M, Bourne-Branchu V, Kempf-Lépine A-S, et al. Deterioration of Physical Activity Level and Metabolic Risk Factors After Early-Stage Breast Cancer Diagnosis. *Cancer Nurs* (2015) 38:E1–9. doi: 10.1097/NCC.0000000000000187
32. Holick CN, Newcomb PA, Trentham-Dietz A, Titus-Ernstoff L, Bersch AJ, Stampfer MJ, et al. Physical Activity and Survival After Diagnosis of Invasive Breast Cancer. *Cancer Epidemiol Biomarkers Prev* (2008) 17:379–86. doi: 10.1158/1055-9965.EPI-07-0771
33. Irwin ML, McTiernan A, Manson JE, Thomson CA, Sternfeld B, Stefanick ML, et al. Physical Activity and Survival in Postmenopausal Women With Breast Cancer: Results From the Women's Health Initiative. *Cancer Prev Res (Phila)* (2011) 4:522–9. doi: 10.1158/1940-6207.CAPR-10-0295
34. Golubic R, May AM, Benjaminsen Borch K, Overvad K, Charles M-A, Diaz MJT, et al. Validity of Electronically Administered Recent Physical Activity Questionnaire (RPAQ) in Ten European Countries. *PloS One* (2014) 9:e92829. doi: 10.1371/journal.pone.0092829
35. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. *J Natl Cancer Inst* (1993) 85:365–76. doi: 10.1093/jnci/85.5.365
36. Gentile S, Delarozière JC, Favre F, Sambuc R, San Marco JL. Validation of the French "Multidimensional Fatigue Inventory" (MFI 20). *Eur J Cancer Care (Engl)* (2003) 12:58–64. doi: 10.1046/j.1365-2354.2003.00295.x
37. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of Physical Activities: An Update of Activity Codes and MET Intensities. *Med Sci Sports Exerc* (2000) 32:S498–504. doi: 10.1097/00005768-200009001-00009
38. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS Statement: Guidelines for the Six-Minute Walk Test. *Am J Respir Crit Care Med* (2002) 166:111–7. doi: 10.1164/ajrccm.166.1.at1102
39. Arcuri JF, Borghi-Silva A, Labadessa IG, Sentanin AC, Candolo C, Pires Di Lorenzo VA. Validity and Reliability of the 6-Minute Step Test in Healthy Individuals: A Cross-Sectional Study. *Clin J Sport Med* (2016) 26:69–75. doi: 10.1097/JSM.0000000000000190
40. Chavez-MacGregor M, Niu J, Zhang N, Elting LS, Smith BD, Banchs J, et al. Cardiac Monitoring During Adjuvant Trastuzumab-Based Chemotherapy Among Older Patients With Breast Cancer. *J Clin Oncol* (2015) 33:2176–83. doi: 10.1200/JCO.2014.58.9465
41. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, et al. Primary Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. *Ann Oncol* (2015) 26(Suppl 5):v8–30. doi: 10.1093/annonc/mdv298
42. Jerusalem G, Lancellotti P, Kim S-B. HER2+ Breast Cancer Treatment and Cardiotoxicity: Monitoring and Management. *Breast Cancer Res Treat* (2019) 177:237–50. doi: 10.1007/s10549-019-05303-y
43. Kitayama H, Kondo T, Sugiyama J, Kurimoto K, Nishino Y, Kawada M, et al. High-Sensitive Troponin T Assay can Predict Anthracycline- and Trastuzumab-Induced Cardiotoxicity in Breast Cancer Patients. *Breast Cancer* (2017) 24:774–82. doi: 10.1007/s12282-017-0778-8
44. Ky B, Putt M, Sawaya H, French B, Januzzi JL, Sebag IA, et al. Early Increases in Multiple Biomarkers Predict Subsequent Cardiotoxicity in Patients With Breast Cancer Treated With Doxorubicin, Taxanes, and Trastuzumab. *J Am Coll Cardiol* (2014) 63:809–16. doi: 10.1016/j.jacc.2013.10.061
45. Wallace KB, Hausner E, Herman E, Holt GD, MacGregor JT, Metz AL, et al. Serum Troponins as Biomarkers of Drug-Induced Cardiac Toxicity. *Toxicol Pathol* (2004) 32:106–21. doi: 10.1080/01926230490261302
46. Mokuyasu S, Suzuki Y, Kawahara E, Seto T, Tokuda Y. High-Sensitivity Cardiac Troponin I Detection for 2 Types of Drug-Induced Cardiotoxicity in Patients With Breast Cancer. *Breast Cancer* (2015) 22:563–9. doi: 10.1007/s12282-014-0520-8

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

SYSTEMATIC REVIEW
published: 21 January 2022
doi: 10.3389/fonc.2021.829875

# Efficacy of Antiresorptive Drugs on Bone Mineral Density in Post-Menopausal Women With Early Breast Cancer Receiving Adjuvant Aromatase Inhibitors: A Systematic Review of Randomized Controlled Trials

*Alessandro de Sire[1]*, Lorenzo Lippi[2], Konstantinos Venetis[3,4], Stefania Morganti[3,5], Elham Sajjadi[3,4], Claudio Curci[6], Antonio Ammendolia[1], Carmen Criscitiello[4,5], Nicola Fusco[3,4] and Marco Invernizzi[2,7]*

*[1] Department of Medical and Surgical Sciences, University of Catanzaro "Magna Graecia", Catanzaro, Italy, [2] Physical and Rehabilitative Medicine, Department of Health Sciences, University of Eastern Piedmont "A. Avogadro", Novara, Italy, [3] Division of Pathology, IEO, European Institute of Oncology IRCCS, Milan, Italy, [4] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy, [5] Division of Early Drug Development, IEO, European Institute of Oncology IRCCS, Milan, Italy, [6] Physical Medicine and Rehabilitation Unit, Department of Neurosciences, ASST Carlo Poma, Mantova, Italy, [7] Translational Medicine, Dipartimento Attività Integrate Ricerca e Innovazione (DAIRI), Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy*

**Background:** Cancer treatment-induced bone loss (CTIBL) is a frequent complication of breast cancer therapies affecting both disability and health-related quality of life (HRQoL). To date, there is still a lack of consensus about the most effective approach that would improve bone health and HRQoL. Therefore, the aim of this systematic review of randomized controlled trials (RCTs) was to summarize the evidence on the effects of antiresorptive drugs on CTIBL in patients with early breast cancer.

**Methods:** PubMed, Scopus, and Web of Science databases were systematically searched up to April 30, 2021 to identify RCTs satisfying the following PICO model: P) Participants: postmenopausal women with early breast cancer receiving adjuvant aromatase inhibitors (AI), age >18 years; I) Intervention: antiresorptive drugs (i.e. bisphosphonates and/or denosumab); C) Comparator: any comparator; O) Outcome: bone mineral density (BMD) modifications. Moreover, a quality assessment was performed according to the Jadad scale.

**Results:** Out of the initial 2415 records, 21 papers (15 studies) were included in the data synthesis. According to the Jadad scale, 6 studies obtained a score of 5, 1 study obtained a score of 4, 13 studies obtained a score of 3, and 1 study with score 1. Although both bisphosphonates and denosumab showed to increase BMD, only denosumab showed significant advantages on fractures.

OPEN ACCESS

**Edited by:**
*Julio de la Torre, Comillas Pontifical University, Spain*

**Reviewed by:**
*Silvia Migliaccio, Foro Italico University of Rome, Italy*
*Richard De Boer, Peter MacCallum Cancer Centre, Australia*

***Correspondence:**
*Alessandro de Sire*
*alessandro.desire@unicz.it*

**Specialty section:**
*This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology*

**Received:** *06 December 2021*
**Accepted:** *30 December 2021*
**Published:** *21 January 2022*

**Citation:**
*de Sire A, Lippi L, Venetis K, Morganti S, Sajjadi E, Curci C, Ammendolia A, Criscitiello C, Fusco N and Invernizzi M (2022) Efficacy of Antiresorptive Drugs on Bone Mineral Density in Post-Menopausal Women With Early Breast Cancer Receiving Adjuvant Aromatase Inhibitors: A Systematic Review of Randomized Controlled Trials. Front. Oncol. 11:829875. doi: 10.3389/fonc.2021.829875*

**Conclusions:** Bone health management in patients with early breast cancer receiving adjuvant AIs remains challenging, and the optimal therapeutic approach is not standardized. Further studies are needed to investigate CTIBL, focusing on both the need for antiresorptive drugs and their duration based on individual patients' characteristics.

**Systematic Review Registration:** https://www.crd.york.ac.uk/prospero, identifier CRD42021267107.

**Keywords: breast cancer, early breast cancer, bone health, quality of life, osteoporosis, rehabilitation**

## INTRODUCTION

Breast cancer (BC) is the most prevalent malignancy in women worldwide, with incidence increasing in last decades (1). Oppositely, mortality from BC decreased in last years, due to the significant advancements in screening programs and therapeutical interventions (2). In response to the progressive increase of women living after a diagnosis of BC, survivorship issues related to cancer treatment and its impact on bone health and health-related quality of life (HRQoL) have progressively emerged (3–9).

Cancer treatment-induced bone loss (CTIBL) is a frequent side effect of the pharmacotherapy used for treating BC. While chemotherapy might lead to an unspecific increase in bone resorption, hormone therapies (HT) reduce residual serum endogenous estrogen levels, with a consequent decrease in bone mineral density (BMD) and an increase in fragility fracture risk (10–17). To date, aromatase inhibitors (AI) are considered the gold standard adjuvant therapy for postmenopausal women with hormone receptor (HR)-positive early BC (EBC) (18, 19). In such patients, a significant decrease in bone density has been observed (20, 21). To counter bone loss induced by AIs in BC patients, several anti-resorptive molecules have been investigated (22, 23). The ZO-FAST study supported the efficacy of zoledronic acid in increasing BMD in postmenopausal women receiving adjuvant AIs (24). In addition, the ABCSG-12 trial showed that zoledronic acid along with endocrine therapy could also increase disease-free survival (DFS) in premenopausal women with EBC (25). In 2015, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published a meta-analysis of individual patient data investigating bisphosphonates (BPs) in the adjuvant setting of EBC, including data from 18,766 women in 26 trials. All tumor subtypes and adjuvant treatments were considered. Use of BPs reduced both bone recurrence (rate ratio [RR] 0.83; p=0.004) and bone fractures (RR: 0.85; p=0.02), with a significant impact also on distant recurrence (RR 0.92; p=0.03) and BC mortality (RR 0.91; p=0.04). Notably, the subgroup analysis showed how the added value of bisphosphonate is limited in premenopausal patients, while postmenopausal patients derived a greater benefit in all outcomes.

Denosumab, a fully human IgG2 monoclonal antibody, has been proposed to treat CTIBL in BC patients undergoing HT not only by improving BMD but also by reducing the rate of clinical fragility fractures (both hip and vertebrae) (12, 26, 27).

Although the long-term management of bone health in BC patients through the combination of different pharmacological therapies is gaining interest, most studies conducted to date have only assessed the effects of a single drug in terms of BMD improvement or fracture risk reduction (28–30). Thus, the gap of knowledge about tailored and effective bone health interventions is far from being understood.

Therefore, this systematic review aims to summarize the current evidence on the efficacy of anti-resorptive agents and their impact on bone health and HRQoL in post-menopausal patients with EBC receiving adjuvant AIs.

## MATERIALS AND METHODS

### Study Registration

This systematic review of randomized controlled trials (RCTs) has been performed ethically in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (31). The PRISMA Checklist is provided as Supplementary Material. A protocol was developed before study initiation and submitted to PROSPERO (https://www.crd.york.ac.uk/prospero; registration number CRD42021267107).

### Search Strategy

We systematically searched PubMed/Medline, Scopus, and Web of Science for RCTs published up to April 30, 2021. Two investigators independently searched the databases. The search strategy is reported in **Table 1**.

### Selection Criteria

In accordance with the PICO model (32), we considered eligible RCTs satisfying the following criteria:

1. P) Participants: postmenopausal women with early BC receiving adjuvant AI, age >18 years;
2. I) Intervention: antiresorptive drugs (i.e. BPs and/or denosumab);
3. C) Comparator: any comparator;
4. O) Outcome: BMD modifications.

Only RCTs published in International journals in English language were included. The exclusion criteria were: i) studies involving animals; ii) language other than English; iii)

**TABLE 1** | Search strategy.

| |
|---|
| ***PubMed*** |
| ((Breast cancer[Title/Abstract]) OR Breast cancer [MeSH Terms]) OR ((aromatase inhibitors [Title/Abstract]) OR aromatase inhibitors [MeSH Terms]) AND (((((osteoporosis [Title/Abstract]) OR bisphosphonate[Title/Abstract]) OR zoledronic acid[Title/Abstract]) OR Denosumab[Title/Abstract]) OR ((((osteoporosis [Title/Abstract]) OR bisphosphonate[MeSH Terms]) OR zoledronic acid[MeSH Terms]) OR Denosumab [MeSH Terms])) AND (((((fracture [Title/Abstract]) OR bone mineral density [Title/Abstract]) OR pain [Title/Abstract]) OR HRQoL [Title/Abstract]) OR ((((fracture [MeSH Terms]) OR bone mineral density [MeSH Terms]) OR pain [MeSH Terms]) OR HRQoL [MeSH Terms])) |
| ***Scopus*** |
| TITLE-ABS-KEY (breast cancer AND aromatase inhibitors AND (osteoporosis OR bisphosphonate OR zoledronic acid OR Denosumab) AND (fracture OR bone mineral density OR pain OR HRQoL) |
| ***Web of Science*** |
| (breast cancer AND aromatase inhibitors AND (osteoporosis OR bisphosphonate OR zoledronic acid OR Denosumab) AND (fracture OR bone mineral density OR pain OR HRQoL)) |

participants with pregnancy; iv) cancer different of BC; v) studies involving patients with metastatic BC; vi) conference abstracts.

After duplication removal, two investigators independently reviewed the title and abstracts of retrieved articles to choose relevant articles. A third reviewer was asked in case of disagreement.

## Data Extraction and Synthesis

Data were assessed and extracted from full-text documents by two independent reviewers (AdS and LL). Any disagreement was solved by discussion or consulting a third reviewer (MI).

The following data were extracted: 1) title and trial name; 2) authors; 3) publication year; 4) number of patients included; 5) intervention characteristics; 6) comparator arm(s); 7) bone-health related outcomes; 8) follow-up.

A descriptive approach was used to synthesize both study characteristics and data extracted. Subgroup analysis has been performed based on the specific drug assessed in the studies included.

## Study Quality and Risk of Bias

Study quality was assessed according to the Jadad scale by two reviewers independently (33). In case of disagreement, a third reviewer was involved in the decisional process to achieve consensus. The clinical trials with a Jadad score between 3 and 5 points were considered as high-quality studies.

# RESULTS

## Main Characteristics of the Included Studies

A total of 2416 records were identified from the search process (PubMed/Medline: 1703 records; Web of Science: 463 records; Scopus: 250 records) and 22 records were identified by reference lists of primary studies. After duplication removal, 1992 records were screened for title and abstract. Therefore, 1857 records were excluded, and 135 full-text studies were screened. One hundred and seventeen records were excluded for not satisfying the eligibility criteria. Finally, the following 21 papers (15 RCTs) were included in the present systematic review: Livi (2019) (29), Gnant (2015) (34), Gnant (2019) (35), Hines (2009) (36), Wagner-Johnston (2015) (37), Greenspan (2015) (38), Coleman (2013) (39), Rhee (2013) (40), Lester (2008) (41), Lester (2012) (42), Takahashi (2012) (43), Llombart (2012) (44), Van Poznak (2010) (45), Markopoulos (2010) (46), Eidtmann (2010) (47), Brufsky (2009) (48), Ellis (2008) (49), Bundred (2008) (24), Brufsky (2008) (50), Brufsky (2012) (51), Safra (2011) (52). Further details on the identification and inclusion/exclusion of the screened studies are reported in **Figure 1**.

Main characteristics of the 15 clinical trials (21 papers) included (24, 29, 34, 35, 39–44, 46–52) are summarized in **Table 2**. These RCTs were published between 2008 (24, 41, 49, 50) and 2019 (29, 35). Most of them (7; 46.7%) were International collaborations (24, 34, 35, 39, 44, 45, 47–51), whereas 3 studies were carried out in Europe (1 in the United Kingdom (41, 42), 1 in Italy (35), 1 in Greece (46)), 3 in Asia (1 in Japan (43), 1 in Korea (40), 1 in Israel (52)) and 2 in the USA (36–38).

Number of patients included ranged from 50 (41) to 3420 (34, 35) subjects. Seven RCTs (24, 36, 37, 39, 43, 44, 47, 48, 50–52) assessed participants who were treated with letrozole, 3 RCTs (41, 42, 45, 46) enrolled patients receiving anastrozole, one RCT (40) included patients treated with anastrozole or letrozole, and in 4 RCTs (29, 34, 35, 38, 49) patients were treated with anastrozole, letrozole, or exemestane.

BC patients received denosumab in 2 studies (26, 34, 35), zoledronic acid in 7 studies (24, 36, 37, 39, 43, 44, 47, 48, 50–52), risedronate in 3 studies (38, 45, 46), ibandronate in 2 studies (29, 41, 42), and alendronate in only one study (40). The comparator arm consisted in no treatment in two studies (46, 52), delayed treatment in 6 studies (24, 36, 37, 39–44, 47, 48, 50–52), and placebo in 7 studies (29, 34, 35, 38, 45, 49).

## Alendronate

From the studies included in this systematic review, only one assessed oral alendronate 5 mg in addition to calcitriol 0.5 μg daily in patients with EBC receiving adjuvant anastrozole or letrozole (40). The study showed significant differences between alendronate and placebo groups in terms of lumbar BMD (-0.5 ± 0.6% vs -3.5 ± 0.6%; p=0.05) at 24 weeks, whereas non-significant improvements were observed in hip BMD (-0.5 ± 0.4% vs -1.3 ± 0.5%; p>0.05). Diverse expression levels were only found in sCTx (72.4%; p<0.05), whereas osteocalcin (OCN) did not show significant differences between groups (29.0%; p>0.05) (as shown by **Table 3**).

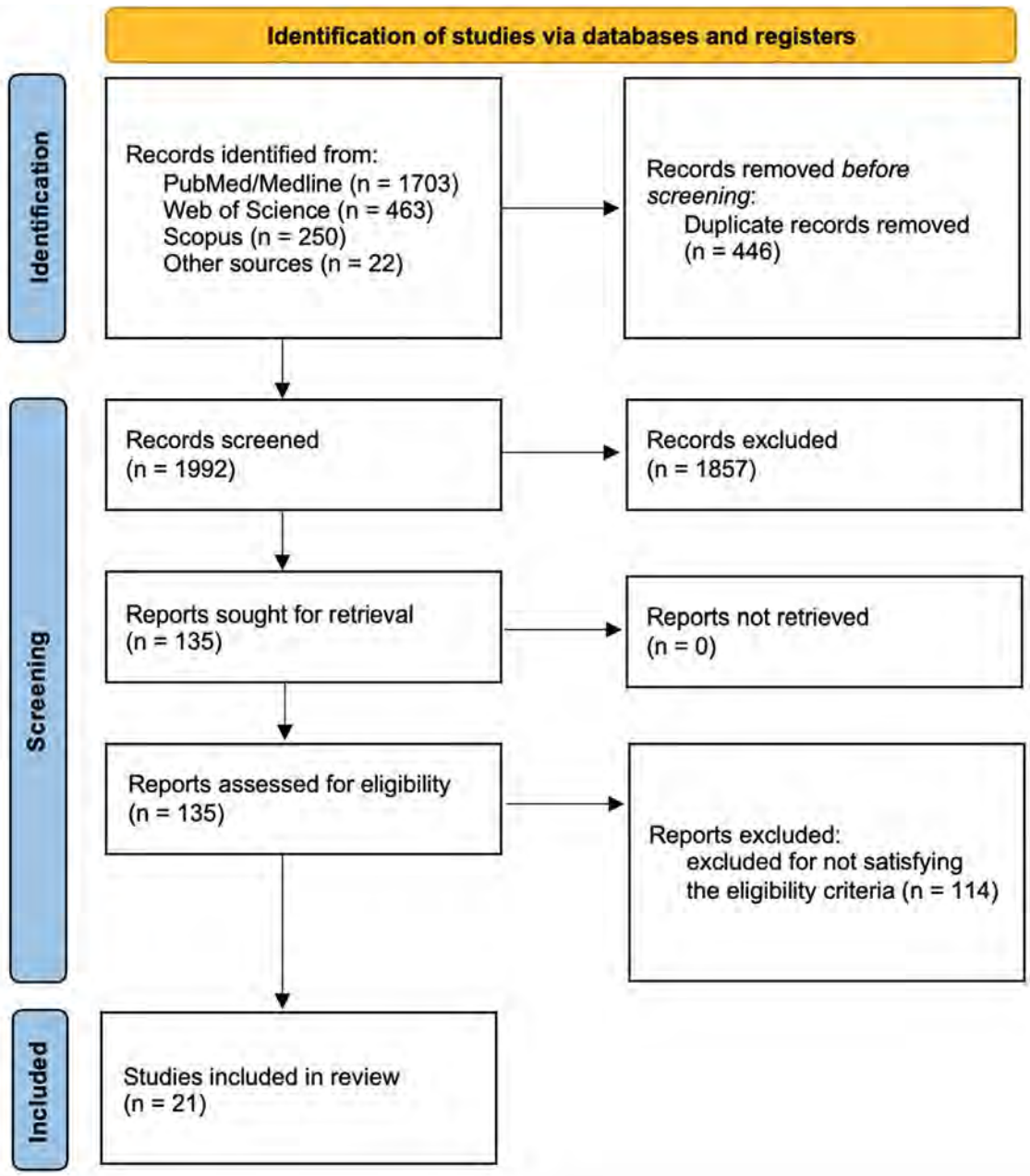



**FIGURE 1** | PRISMA flow diagram.

## Denosumab

Three papers (2 studies) compared six-monthly denosumab 60 mg with placebo, reporting benefits in terms of fracture risk reduction or BMD improvement (34, 35, 49).

Gnant et al., in a collaborative study including 3420 patients, observed consistent differences in fracture incidence between patients treated with denosumab (5%) vs. untreated (9.6%) (34). Moreover, a significant difference in terms of time-to-first clinical fracture, the study primary endpoint, was observed between the two groups (HR 0.5, 95% CI 0.39–0.65, p<0.0001). Oppositely, the study by Ellis and colleagues (49) did not find major differences for fracture outcomes: no vertebral fractures were observed in both groups, the incidence of nonvertebral fractures was 6% in both arms, major nonvertebral fractures were observed in 3 women receiving denosumab (2%) and 5 women receiving placebo (4%).

Intriguingly, the two studies revealed significant differences between groups in terms of BMD. More in detail, Ellis et al. (49)

**TABLE 2 |** Main characteristics of the articles included in the present systematic review.

| Authors | Journal | Publication year | Nationality | Population | Age (years) | Hormonal therapy | Intervention | Comparator | Outcomes | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | ***Alendronate*** | | | | | |
| Rhee et al. (40) | *Endocr J* | 2013 | Korea | n: 98<br>IG: 49<br>CG: 49 | IG: 57.1 ± 1.0<br>CG: 58.5 ± 1.1 | Anastrozole or letrozole | Alendronate 5 mg + calcitriol 0.5 μg daily | Placebo | **- LS BMD**<br>**- TH BMD**<br>- Bone turnover biomarkers<br>- safety | 24 weeks |
| | | | | | ***Denosumab*** | | | | | |
| Ellis et al. (49) (NCT00089661) | *J Clin Oncol.* | 2008 | International Collaboration | n: 252<br>IG: 127<br>CG: 125 | IG: 59.2 ± 8.9<br>CG: 59.7 ± 9.7 | Anastrozole, letrozole, or exemestane | Denosumab 60 mg sc every 6 months | Placebo | **- LS BMD**<br>- TH BMD<br>- FN BMD<br>- Radius BMD<br>- Bone turnover biomarkers<br>- Vertebral and nonvertebral fractures<br>- Safety<br>- Overall survival | 24 months |
| Gnant et al. (34) (ABCSG-18) | *The Lancet* | 2015 | International Collaboration | n: 3420<br>IG: 1711<br>CG: 1709 | 64 (38 – 91) | Anastrozole, letrozole, or exemestane | Denosumab 60 mg sc every 6 months | Placebo | **- Time to first fracture**<br>- Vertebral and nonvertebral fractures<br>- LS BMD<br>- TH BMD<br>- FN BMD<br>- Disease-free survival<br>- Bone-metastasis free survival<br>- Overall survival | 36 months |
| Gnant et al. (35) (ABCSG-18) | *Lancet Oncol.* | 2019 | International Collaboration | n: 3420<br>IG: 1711<br>CG: 1709 | 64 (38 – 91) | Anastrozole, letrozole, or exemestane | Denosumab 60 mg sc every 6 months | Placebo | **- Time to first fracture**<br>- Vertebral and nonvertebral fractures<br>- LS BMD<br>- TH BMD<br>- FN BMD<br>- Disease-free survival<br>- Bone-metastasis free survival<br>- Overall survival | 96 months |
| | | | | | ***Ibandronate*** | | | | | |
| Lester et al. (41) (ARIBON) | *Clinical Cancer Research* | 2008 | UK | n: 50<br>IG: 25<br>CG: 25 | IG: 67.8 (58.9- | Anastrozole | Ibandronate 150 mg every month | Placebo | **- LS BMD**<br>**- TH BMD**<br>- Bone | 24 months |

*(Continued)*

**TABLE 2** | Continued

| Authors | Journal | Publication year | Nationality | Population | Age (years) | Hormonal therapy | Intervention | Comparator | Outcomes | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 73.4) CG: 67.5 (63.6-71.0) | | | | turnover biomarkers - Safety | |
| Lester et al. (42) (ARIBON) | *Journal of Bone Oncology* | 2012 | UK | n: 50 IG: 25 CG: 25 | IG: 67.8 (58.9-73.4) CG: 67.5 (63.6-71.0) | Anastrozole | Ibandronate 150 mg every month for 24 months | Ibandronate 150 mg every month started after 24 months | **- LS BMD** **- TH BMD** | 60 months |
| Livi et al. (29) (BONADIUV) | *European Journal of Cancer* | 2019 | Italy | n: 144 IG: 89 CG: 82 | IG: 60.5 (54.3-67.0) CG: 59.6 (53.9-68.0) | Anastrozole, letrozole, or exemestane | Ibandronate 150 mg every month | Placebo | **- LS BMD** **- TH BMD** - Safety - Disease recurrence - Overall survival | 24 months |
| | | | | | | ***Risedronate*** | | | | |
| Greenspan et al. (38) (NCT00485953) | *Osteoporosis International* | 2015 | USA | n: 109 IG: 55 CG: 54 | IG: 65 ± 1 CG: 64 ± 1 | Anastrozole, letrozole, or exemestane | Risedronate 35 mg every week | Placebo | - **LS BMD** **- TH BMD** - FN BMD - TB BMD - Bone turnover biomarkers | 24 months |
| Markopoulos et al. (46) (ARBI) | *Breast Cancer Research* | 2010 | Greece | n: 70 IG: 37 CG: 33 | IG: 62.6 ± 8.5 CG: 64.5 ± 9.2 | Anastrozole | Risedronate 35 mg every week | No treatment | - **LS BMD** **- TH BMD** | 24 months |
| Van Poznak et al. (45) (SABRE) | *Journal of Clinical Oncology* | 2010 | International Collaboration | n: 154 IG: 77 CG: 77 | IG: 63.8 CG: 64.8 | Anastrozole | Risedronate 35 mg every week | Placebo | **- LS BMD** - TH BMD - Bone turnover biomarkers | 24 months |
| | | | | | | ***Zoledronate*** | | | | |
| Brufsky et al. (52) | *The Oncologist* | 2008 | International Collaboration | n: 1667 IG: 833 CG: 834 | IG: 58 (35-87) CG: 59 (37-89) | Letrozole | Immediate zoledronate 4 mg iv every 6 months | Delayed zoledronate 4 mg iv every 6 months | **- LS BMD** - TH BMD - Bone turnover biomarkers - Disease recurrence - Safety | 12 months |
| Brufsky et al. (48) (Z-FAST) | *Clinical Breast Cancer* | 2009 | International Collaboration | n: 602 IG: 301 CG: 301 | IG: 61.5 ± 9.33 CG: 61 ± 8.92 | Letrozole | Immediate zoledronate 4 mg iv every 6 months | Delayed zoledronate 4 mg iv every 6 months | - **LS BMD** - TH BMD - Bone turnover biomarkers - Vertebral and nonvertebral fractures - Disease recurrence | 36 months |

*(Continued)*

**TABLE 2** | Continued

| Authors | Journal | Publication year | Nationality | Population | Age (years) | Hormonal therapy | Intervention | Comparator | Outcomes | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| Brufsky et al. (50) (Z-FAST) | *Cancer* | 2012 | International Collaboration | n: 602 IG: 301 CG: 301 | IG: 61.5 ± 9.33 CG: 61 ± 8.92 | Letrozole | Immediate zoledronate 4 mg iv every 6 months | Delayed zoledronate 4 mg iv every 6 months | - **LS BMD** - TH BMD - Bone turnover biomarkers - Vertebral and nonvertebral fractures - Disease recurrence | 60 months |
| Bundred et al. (24) (ZO-FAST) | *Cancer* | 2008 | International Collaboration | n: 1065 IG: 532 CG: 533 | IG: 57 (36-87) CG: 58 (37-81) | Letrozole | Immediate zoledronate 4 mg iv every 6 months | Delayed zoledronate 4 mg iv every 6 months | **- LS BMD** - TH BMD - Bone turnover biomarkers - Safety | 12 months |
| Eidtmann et al. (47) (ZO-FAST) | *Ann Oncol.* | 2010 | International Collaboration | n: 1065 IG: 532 CG: 533 | IG: 57 (36-87) CG: 58 (37-81) | Letrozole | Immediate zoledronate 4 mg iv every 6 months | Delayed zoledronate 4 mg iv every 6 months | **- LS BMD** - TH BMD - Vertebral and nonvertebral fractures - Disease recurrence - Overall survival - Safety | 36 months |
| Coleman et al. (39) (ZO-FAST) | *Ann Oncol.* | 2013 | International Collaboration | n: 1065 IG: 532 CG: 533 | IG: 57 (36-87) CG: 58 (37-81) | Letrozole | Immediate zoledronate 4 mg ev every 6 months | Delayed zoledronate 4 mg ev every 6 months | **- LS BMD** - TH BMD - Vertebral and nonvertebral fractures - disease recurrence - overall survival - safety | 60 months |
| Llombart et al. (44) (E-ZO-FAST) | *Clinical Breast Cancer* | 2012 | International Collaboration | n: 522 IG: 252 CG: 270 | IG: 58 (40-81) CG: 58 (44-78) | Letrozole | Immediate zoledronate 4 mg iv every 6 months | Delayed zoledronate 4 mg iv every 6 months | **- LS BMD** - TH BMD - Vertebral and nonvertebral fractures - disease recurrence - safety | 12 months |
| Safra et al. (51) (NCT00376740) | *Oncology* | 2011 | Israel | n: 86 IG: 47 CG: 39 | IG: 59.08 ± 8.5 CG: 61.18 ± 9.2 | Letrozole following Tamoxifen | Immediate zoledronate 4 mg iv every 6 months | No treatment | **- LS BMD** - TH BMD - Vertebral and nonvertebral fractures - Disease recurrence - Overall survival | 48 months |
| Takahashi et al. (43) | *Breast Cancer Research and Treatment* | 2012 | Japan | n: 194 IG: 97 CG: 97 | IG: 61.47 ± 6.80 CG: | Letrozole | Immediate zoledronate 4 mg iv every 6 months | Delayed zoledronate 4 mg iv every 6 months | **- LS BMD** - TH BMD - Bone turnover | 12 months |

*(Continued)*

**TABLE 2** | Continued

| Authors | Journal | Publication year | Nationality | Population | Age (years) | Hormonal therapy | Intervention | Comparator | Outcomes | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 60.45 ± 6.56 | | | | biomarkers - Vertebral and nonvertebral fractures | |
| Hines et al. (36) N03CC (Alliance) trial) | *Breast Cancer Res Treat.* | 2009 | USA | n: 551 IG: 274 CG: 277 | IG: 59.2 ± 11.20 CG: 59.6 ± 10.25 | Letrozole | Upfront zoledronate 4 mg iv every 6 months | Delayed zoledronate 4 mg iv every 6 months | **- LS BMD** - TH BMD - FN BMD - Vertebral and nonvertebral fractures - toxicity | 24 months |
| Wagner-Johnston et al. (37) (N03CC (Alliance) trial) | *Cancer* | 2015 | USA | n: 551 IG: 274 CG: 277 | IG: 59.2 ± 11.20 CG: 59.6 ± 10.25 | Letrozole | Upfront zoledronate 4 mg iv every 6 months | Delayed zoledronate 4 mg iv every 6 months | **- LS BMD** - TH BMD - FN BMD - Vertebral and nonvertebral fractures - toxicity | 60 months |

*BMD, bone mineral density; CG, control group; FN, femoral neck; IG, intervention group; iv, intravenous; FN, femoral neck; LS, lumbar spine; sc, subcutaneous; TB, total body; TH, total hip; UK, United Kingdom; USA, United States of America.*
*Primary outcomes of the study included were marked in bold.*

reported significant differences between groups after 2 years of treatment (12 months: 5.5%; p<0.0001; 24 months: 7.6%; p<0.0001). On the other hand, hip BMD increased accordingly in both TH site (12 months: p<0.0001; 24 months: 4.7%; p<0.0001) and FN site (12 months: p<0.0001; 24 month: 3.6%; p<0.0001). Similarly, Gnant et al. (34, 35) underlined a significant difference between groups at 36 months (12 months: -1.81% vs +3.94%; p<0.0001; 24 months: -2.44% vs +5.85%; p<0.0001; 36 months: -2.75% vs +7.27%; p<0.0001). Hip BMD results were in line with the previous results with a significant increase in the denosumab group (12 months: -1.20% vs +2.67%; p<0.0001; 24 months: -2.5% vs +3.70%; p<0.0001; 36 months: -3.32% vs +4.60%; p<0.0001). Modifications in bone turnover were suggested by Ellis et al. (49), reporting significant differences between groups in C-telopeptide I (sCTx) and procollagen type I N-terminal peptide (P1NP), two markers of bone remodeling (1 month: CTX: -9% vs -91%; p<0.0001; P1NP: -2% vs -29%; p<0.0001). On the contrary, joint pain, back pain, bone pain and fatigue showed no differences when the two groups were compared. Outcomes are reported in detail in **Table 3**.

## Ibandronate

The effect of another anti-resorptive drug (i.e., ibandronate 150 mg every month) was assessed in BC survivors receiving anastrozole (41, 42) and anastrozole, letrozole, and exemestane (29). The study of Lester et al. in 2008 assessed the effects of Ibandronate (150 mg every month) for 24 months compared to placebo in osteopenic patients (41). On the other hand, patients with normal BMD did not receive any therapy while patients with osteoporosis received Ibandronate 150 mg every month. Interestingly, no fractures were recorded during the first 2 years (41). After 2 years, 3/20 patients continued to receive BPs over the next 3 years, while 8 patients received delayed ibandronate treatment. At 60 months, BMD changes were reported without reporting significant differences between groups (LS BMD: -2.88 vs 0.29%; p=NR; TH BMD: 1.18% vs -3.71%; p=NR). On the other hand, the study conducted by Lester et al. in 2012 recorded 4 fractures in the group that received ibandronate for 2 years, while the group treated with ibandronate after 2 years showed 3 fractures (42). In total, 10 fragility fractures were recorded: 4 fractures in the group treated with ibandronate for 2 years, 3 fractures in the placebo group treated with ibandronate after 2 years, and further 3 fractures in the osteoporotic group treated with ibandronate for 5 years.

Variations in lumbar and hip BMD were chosen as primary outcomes in both the ARIBON (41, 42) and BONADIUV trials (29). In both of them significant differences were found between ibandronate and placebo treated patients at both lumbar BMD and hip BMD after 12 and 24 months (29, 41). In particular, Lester et al. (41, 42) reported significant differences between groups in LS BMD (12 months: -3.19% vs +1.49%; p=0.012; 24 months: -3.22% vs +2.98%; p=0.002) and in TH BMD (12 months: -2.27 vs +0.98; p=0.001; 24 months: -3.90% vs +0.60%; p=0.003). Accordingly, Livi et al. (29) reported significant differences between groups (LS BMD 12 months: -2.29% vs +2.96%; p=0.021; 24 months: -4.22% vs +6.09%; p<0.0001; TH BMD: 12 months: -2.35% vs +3.11%; p<0.001; 24 months: -1.51% vs +4.64%; p=0.09).

Bone turnover biomarkers (sCTx, NTX, and bALP) were assessed instead only in the ARIBON study, with significant differences (NTX 12 months: +39.5% vs -30.9%; p<0.001; sCTx 12 months: +34.9% vs -26.3%; p<0.001; bALP 12 months: +37.0% vs -22.8%; p<0.001) (41). **Table 3** reported further details.

**TABLE 3 |** Main results of the articles included in the present systematic review.

| Study | Fractures | LS BMD | TH BMD | FN BMD | Bone turnover biomarkers | Pain | Fatigue | Anxiety and Depression | Weakness | Lymphedema |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Alendronate*** | | | | | | | | | | |
| Rhee et al. (40) | NR | **24 weeks: -3.5 ± 0.6% vs -0.5 ± 0.6%; p=0.05** | **24 weeks: -1.3 ± 0.5% vs -0.5 ± 0.4%; p=NS** | NR | sCTx 24 weeks: 72.4%; p<0.05 OCN 24 weeks: 29.0%; p=NS | NR | NR | NR | NR | NR |
| ***Denosumab*** | | | | | | | | | | |
| Ellis et al. (49) | 4% vs 2% p=NR | **12 months: 5.5%; p<0.0001** 24 months: 7.6%; p<0.0001 | 12 months: p<0.0001 24 months: 4.7%; p<0.0001 | 12 months: p<0.0001 24 month: 3.6%; p<0.0001 | 1 month: sCTx 1 month: -9% vs -91%; p<0.0001 1 month: P1NP 1 month: -2% vs -29%; p<0.0001 | Articular pain: 25% vs 24%; p=NR Back pain: 12.5% vs 14%; p=NR | 14.2% vs 13.2%; p=NR | NR | NR | NR |
| Gnant et al. (34) | Incidence: 9.6% vs 5%; p=NR **Time to first fracture: HR 0.5 [95% CI 0.39–0.65], p<0·0001** | 12 months: -1.81% vs +3.94%; p<0.0001 24 months: -2.44% vs +5.85%; p<0.0001 36 months: -2.75% vs +7.27%; p<0.0001 | 12 months: -1.20% vs +2.67%; p<0.0001 24 months: -2.5% vs +3.70%; p<0.0001 36 months: -3.32% vs +4.60%; p<0.0001 | 12 months: -1.08% vs +2.22%; p<0.0001 24 months: -2.33% vs +2.86%; p<0.0001 36 months: -3.10% vs +3.41%; p<0.0001 | NR | Articular pain: 26% vs 26% p=NS Back pain: 9% vs 9% p=NS Bone pain: 7% vs 8% p=NS | 6% vs 6%; p=NS | NR | NR | NR |
| Gnant et al. (35) | Incidence: 9.6% vs 5%; p=NR **Time to first fracture: HR 0.5 [95% CI 0.39–0.65], p<0·0001** | 12 months: -1.81% vs +3.94%; p<0.0001 24 months: -2.44% vs +5.85%; p<0.0001 36 months: -2.75% vs +7.27%; p<0.0001 | 12 months: -1.20% vs +2.67%; p<0.0001 24 months: -2.5% vs +3.70%; p<0.0001 36 months: -3.32% vs +4.60%; p<0.0001 | 12 months: -1.08% vs +2.22%; p<0.0001 24 months: -2.33% vs +2.86%; p<0.0001 36 months: -3.10% vs +3.41%; p<0.0001 | NR | Articular pain: 26% vs 26% p=NS Back pain: 9% vs 9% p=NS Bone pain: 7% vs 8% p=NS | 6% vs 6%; p=NS | NR | NR | NR |
| ***Ibandronate*** | | | | | | | | | | |
| Lester et al. (41) | No fractures | 12 months: -3.19% vs +1.49%; p=0.012 24 months: -3.22% vs +2.98%; p=0.002 | 12 months: -2.27 vs +0.98; p=0.001 24 months: -3.90% vs +0.60%; p=0.003 | NR | NTX 12 months: +39.5% vs -30.9%; p<0.001 sCTx 12 months: +34.9% vs -26.3%; p<0.001 bALP 12 months: +37.0% vs -22.8%; p<0.001 | NR | NR | NR | NR | NR |
| Lester et al. (42) | 3 vs 4; p=NR | 60 months -2.88 vs 0.29%; p=NR | 60 months 1.18% vs -3.71%; p=NR | NR | NR | NR | NR | NR | NR | NR |
| Livi et al. (29) | NR | 12 months: -2.29% vs +2.96%; p=0.021 | 12 months: -2.35% vs +3.11%; p<0.001 | NR | NR | NR | NR | NR | NR | NR |

*(Continued)*

**TABLE 3** | Continued

| Study | Fractures | LS BMD | TH BMD | FN BMD | Bone turnover biomarkers | Pain | Fatigue | Anxiety and Depression | Weakness | Lymphedema |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 24 months: -4.22% vs +6.09%; p<0.0001 | 24 months: -1.51% vs +4.64%; p=0.09 | | | | | | | |
| | | | | | ***Risedronate*** | | | | | |
| Greenspan et al. (38) | NR | 12 months: -1.2% vs +2%; p<0.0001 **24 months: -1.7% vs +2.3%; p<0.0001** | 12 months: -1.6% vs +0.5%; p<0.0001 **24 months: -2.7% vs +0.6%; p<0.0001** | 24 months: 2.6 ± 0.8%; p=0.0009 | sCTx 12 months: p<0.01 sCTx 24 months: p<0.01 P1NP 12 months: p<0.0001 P1NP 24 months: p<0.0001 | NR | NR | NR | NR | NR |
| Markopoulos et al. (46) | No fractures | **12 months: 0% vs -0.4%; p=NS** 24 months: -1.5% vs +5.7%; p=0.006 | **12 months: -1.3% vs 0%; p=NS** 24 months: -3.9% vs +1.6%; p=0.037 | NR | NR | NR | NR | NR | NR | NR |
| Van Poznak et al. (45) | 5 (2.1%) | **12 months: -1.2% vs +1.2%; p<0.0001** 24 months: -1.8% vs +2.2%; p<0.0001 | 12 months: -0.4% vs +0.9%; p=0.0023 24 months: -1.1% vs +1.8%; p<0.0001 | NR | sCTx 6 months: +8.2% vs -44.0%; p<0.0001 sCTx 12 months: +6.1% vs -43.8%; p<0.0001 P1NP 6 months: -1.5% vs -41.8%; p<0.0001 P1NP 12 months: -2.4% vs -44.3%; p<0.0001 bALP 6 months: +1.6% vs -21.6%; p<0.0001 bALP 6 months: +3.9% vs -22.7%; p<0.0001 | Articular pain: 7.8% vs 5.2%; p=NR Bone pain: 1.3% vs 1.3%; p=NR | NR | NR | No weakness | NR |
| | | | | | ***Zoledronate*** | | | | | |
| Brufsky et al. (52) | 2.1% vs 2.2%; p=NR | 12 months: 5.2%; p<0.0001 | 12 months: 3.5%; p<0.0001 | NR | NTX: 33.3%–49%; p<0.0001 BSAP 30.3%–48.9%; p<0.0001 | Articular pain: 28.5% vs 31.7%; p=NR Back pain: 6.2% vs 5.6%; p=NR Bone pain: 5.9% vs 12.2%; p=NR | NR | Depression: 6.7% vs 3.9%; p=NR | NR | NR |

*(Continued)*

**TABLE 3** | Continued

| Study | Fractures | LS BMD | TH BMD | FN BMD | Bone turnover biomarkers | Pain | Fatigue | Anxiety and Depression | Weakness | Lymphedema |
|---|---|---|---|---|---|---|---|---|---|---|
| Brufsky et al. (48) | 6.3% vs 5.7% p=NS | **12 months: 4.3% p<0.0001** 24 months: 6% p<0.0001 36 months: 6.7% p<0.0001 | 12 months: 3.2% p<0.0001 24 months: 4.6% p<0.0001 36 months: 5.3% p<0.0001 | NR | NTX: p=NS BSAP: p=0.0045 | Articular pain: 37% vs 36.3%; p=NS Back pain: 10.7% vs 9.3%; p=NS Bone pain: 6.7% vs 13%; p=0.01 | 22.3% vs 26%; p=NS | Anxiety: 6% vs 4.7%; p=NS Depression: 11.7% vs 8.7%; p=NS | NR | 5.7% vs 5.3%; p=NS |
| Brufsky et al. (50) | 9.3% vs 11%; p=0.3803 | 48 months: p<0.0001 61 months: 8.9% p<0.0001 | 48 months: p<0.0001 61 months: 6.7% p<0.0001 | NR | NTX: p=NS BSAP: p=0.0002 | Articular pain: 47.0% vs 45.3%; p=NR; Back pain: 14.7% vs 17.3%; p=NR Bone pain: 16.0% vs 8.0%; p=NR Myalgia: 20.3% vs 15.7%; p=NR | 33.7% vs 29.3; p=NR | Depression: 11.7% vs 14.0%; p=NR | NR | 12.0% vs 10.0%; p=NR |
| Bundred et al. (24) | 1.7% vs 1.5%; p=NR | **12 months: 5.7%; p<0.0001** | 3.6%; p<0.0001 | NR | BSAP 12 months: 45.6%; p<0.0001 NTX: 33%; p<0.0001 | Articular pain: 29% vs 32.6%; p=NR Back pain: 6.5% vs 5.7%; p=NR Bone pain: 6.9% vs 12.3%; p=NR | 11.4% vs 11.2%; p=NR | Depression: 5.3% vs 2.8%; p=NR | NR | NR |
| Eidtmann et al. (47) | 6% vs 5% p=NS | **12 months: 5.27% p<0.0001** 24 months: 7.94% p<0.0001 36 months: 9.29% p<0.0001 | NR p<0.0001 | NR | NR | Articular pain: 40.7% vs 42.2%; p=NR Back pain: 11.4% vs 10.5%; p=NR Bone pain: 10.1% vs 15.3%; p=NR | 15.1% vs 16%; p=NR | Depression: 6.5% vs 4.8%; p=NR | NR | 5.4% vs 6.5%; p=NR |
| Coleman et al. (39) | NR | 60 months: -5.4% vs +4.3%; p<0.0001 | 60 months: -4.2% vs +1.6%; p<0.0001 | NR | NR | Articular pain: 46.9% vs 49% p=NR Back pain: 15.1% vs 15% p=NR Bone pain: 12.1% vs 18.5% p=NR | 17.8% vs 17.7%; p=NR | NR | NR | NR |
| Llombart et al. (44) | 1.9% vs 0.8%; p=NR | **12 months: 5.43%; p<0.0001** | 12 months: 3.31%; p<0.0001 | NR | NR | Articular pain: 38.9% vs 37.7%; p=NS | 18.5% vs 15.1%; p=NS | Anxiety: 5.2% vs 3.6%; p=NS Depression: | 7.8% vs 9.1%; p=NS | 4.1% vs 5.6%; p=NS |

*(Continued)*

**TABLE 3** | Continued

| Study | Fractures | LS BMD | TH BMD | FN BMD | Bone turnover biomarkers | Pain | Fatigue | Anxiety and Depression | Weakness | Lymphedema |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Back pain: 7% vs 5.2%; p=NS<br>Bone pain: 4.1% vs 8.3%; p=NS p<0.05<br>Shoulder pain: 5.9% vs 4%; p=NS | | 5.6% vs 2%; p=NS | | |
| Safra et al. (51) | 0 vs 0 p=NS | **24 months: 0.84; p<0.0001**<br>**48 months: 0.76; p<0.0001** | 24 months: 0.96; p=0.0041<br>48 months: 0.77; p=0.52 | NR | NR | Articular pain: 26% vs 21%; p=NR | 17% vs 8%; p=NR | 4% vs 0%; p=NR | NR | NR |
| Takahashi et al. (43) | No fractures | **12 months: 4.9%; p<0.0001** | 12 months: 4.4%; p<0.0001 | NR | NTX 6 months: +21.8 vs -6.5%; p=NR<br>NTX 12 months: +9.4% vs -23.6%; p=NR<br>BSAP 6 months: +14.9% vs -33.6%; p=NR<br>BSAP 12 months: +10.2% vs -39.4%; p=NR | Articular pain: 48.5% vs 51.6% p=NS | 11,3% vs 9.6% p=NS | NR | NR | NR |
| Hines et al. (36) | NR | **12 months: 3.66% vs -1.66%; p<0.001**<br>**24 months: 4.94% vs -2.28%; p<0.001** | 12 months: 1.02% vs -1.41%; p<0.001<br>24 months: 1.22% vs -3.34%; p<0.001 | 12 months: 2.08% -0.09%; p<0.001<br>24 months: 3.36% vs 0.54%; p<0.001 | NR | 12 months: Back pain: 25% vs 23%; p=0.67<br>Myalgia: 7% vs 5%; p=0.53<br>Articular pain; 13% vs 11%; p=0.59 | 12 months: 5% vs 2%; p= 0.038 | NR | NR | NR |
| Wagner-Johnston et al. (37) | 25 vs 24; p= 0.84 | **> 5% BMD differences: 10.2% vs 41.2%; p<0.0001** | > 5% BMD differences in both TH and FN BMD: 7.6% vs 45.8%; p<0.0001 | | NR | NR | NR | NR | NR | NR |

*bALP, bone isoforms of alkaline phosphatase; BSAP, bone-specific alkaline phosphatase; CG, control group; C-telopeptide I (sCTx); FN, femoral neck; IG, intervention group; LS, lumbar spine; NR, not reported; NS, not significant; NTx, N-telopeptide; OCN, osteocalcin; P1NP, procollagen type I N-terminal peptide; TH, total hip.*
*Primary outcomes of the study included were marked in bold.*

## Risedronate

The effects of risedronate 35 mg weekly in BC patients treated with anastrozole or letrozole, or exemestane were assessed in three studies (38, 45, 46). No fragility fractures were reported by Markoupolos et al. (46). In the study by Von Poznak et al., four patients in the control arm had fractures versus none in the risedronate arm (45). Lumbar BMD, a primary outcome in all these studies, was significantly increased in all trials after 24 months of treatment with risedronate (38, 45, 46). Similarly, significant differences were reported in hip BMD (38, 45, 46).

When bone turnover biomarkers were evaluated, significant differences between the risedronate and placebo groups were seen in the expression of isoforms of alkaline phosphatase (bALP), sCTx, N-telopeptide (NTX), and P1NP (38, 45). Joint pain was reported only by Van Poznak et al. only (45), without significant differences between groups (see **Table 3** for further details).

## Zoledronate

Seven studies (24, 36, 37, 39, 43, 44, 47, 48, 50–52) assessed the effects of endovenous administration of zoledronate 4 mg every 6 months in BC women treated with adjuvant letrozole. Of note, the study of Wagner-Johnston et al. evaluated EBC patients starting letrozole after completing

tamoxifen treatment (37). Six studies (24, 36, 37, 39, 43, 44, 47, 48, 50, 51) compared the bone protection effect of immediate-start to delayed-start of zoledronic acid administration. On the other hand, Safra et al. (52) compared zoledronic acid administration with a control group not receiving any treatment.

In the delayed arm, zoledronic acid was initiated when BMD decreased to less than -2.0 or when a fragility fracture occurred. Although no differences were detected between the randomized groups regarding fracture incidence, significant effects in terms of both lumbar, the primary endpoint, and hip BMD increase were reported in the early administration group after 12, 24, 36, and 60 months (24, 36, 37, 39, 43, 44, 47, 48, 50, 51) (see **Table 3** for further details).

Bone turnover biomarkers were assessed in three studies, showing positive modifications in the early zoledronate group (24, 43, 48, 50, 51). Only one study did not record significant differences in sCTx concentrations after 36 months (48). Differences in terms of musculoskeletal pain, fatigue, anxiety, depression, weakness, and lymphedema were non-significant or not reported. **Table 3** summarizes the main results of these studies.

## Study Quality

Out of 21 studies included in this analysis, 20 of them (24, 29, 34–44, 47–52) were classified as high quality according to the Jadad scale (53). In particular, 6 papers (28.6%) (34, 35, 38, 40, 45, 49) obtained a score of 5, 1 paper (4.8%) (29) obtained score 4, 13 papers (61.9%) (24, 36, 37, 39, 41–44, 47–52) obtained a score of 3 and 1 paper (4.8%) (46) obtained a score of 1 (further details are depicted in **Table 4**).

# DISCUSSION

AIs are considered the standard adjuvant therapy in postmenopausal women with early HR-positive BC (18, 19). However, the detrimental effect of AIs on bone health might significantly increase the risk of fractures, with negative consequences in terms of HRQoL and disability (54–56). Therefore, the implementation of tailored and effective interventions to reduce bone-related adverse events and preserve bone health is a crucial challenge in the complex management of patients with EBC receiving AIs. Thus, the present systematic review was aimed at summarizing the state of the art about bone-modifying agents to counteract Ais-induced bone loss, to provide data to guide the future research and clinical management of BC survivors.

Our findings pointed out the consistent improvement in BMD after 3 years of denosumab administration (34). Thus, denosumab could be considered among the most effective therapy to improve BMD and reduce fracture risk in EBC patients receiving AIs. Similarly, three RCTs provided long-term evidence (i.e., 5 years) about treatment with zoledronic acid, showing significant results in terms of lumbar and hip BMD improvement (37, 39, 51). Oral BPs also proved to be effective in enhancing BMD, even if the evidence supporting these drugs is weaker, given the smaller cohorts of patients, shorter treatment periods and less consistent results compared to those testing denosumab or zoledronic acid (29, 38, 40–42, 45, 46). Only the recent study from Livi et al. revealed a higher percentage of lumbar BMD improvement in BC survivors that were concomitantly treated with AIs and oral ibandronate compared with placebo (29). Yet, consistent data on the effectiveness of oral BPs on bone health in this setting are still lacking.

Interventions with anti-resorptive agents have also been found to have a positive impact on DFS. In particular, conflicting results were reported in the current literature with the ABCSG-18 trial (35) that underlined promising benefits of denosumab in DFS of post-menopausal early BC women receiving adjuvant aromatase inhibitor therapy. On the other hand, the D-CARE trial, which assessed the effects of denosumab in high-stage BC patients, did not report improvements in bone metastasis-free survival (57).

Similarly, controversial results were reported for BFs. In particular, the GAIN study showed no DFS benefits for both pre-menopausal and peri-menopausal BC patients who received oral ibandronate in the adjuvant treatment (58).

In accordance, large prospective studies assessing BPs failed to underline consistent effects on DFS endpoint in BC survivors (39, 51, 59) while positive data were provided by the EBCTCG meta-analysis reporting positive effects (RR for recurrence 0.86, 95% CI 0.78–0.94, p=0.002 in zoledronic acid arm) but restricted to postmenopausal women only (60). Therefore, to date, there is no consensus in terms of BPs prescription with the aim to improve DFS considering the large heterogeneous and discordant data.

On the other hand, a joint position statement of interdisciplinary cancer and bone societies suggested that adjuvant BPs should be considered in all postmenopausal women at risk for BC recurrence (61). Similarly, the Cancer Care Ontario and the American Society of Clinical Oncology (ASCO) guidelines recommended to consider BP prescription for all patients who are deemed at high enough risk of relapse (62). However, the authors underline that the lack of evidence did not allow a precise subgroups stratification for patients that might have major benefits from BP prescription (62).

Besides the role of BPs in overall and disease-free survival is still controversial, the cost-effectiveness of their routine use in clinical practice is far from being understood (63).

Taken together, these results suggest that the mechanisms underpinning the adjuvant effects of anti-resorptive drugs in patients with BC need to be further investigated.

Moreover, long-term effects of antiresorptive drugs also deserve to be considered. Although comprehensive management of AIs bone loss has been proposed to optimize bone health, to date, few evidence about the long-term effects of anti-osteoporotic treatments is available. International guidelines recommend the administration of anti-resorptive drugs for the whole duration of AIs therapy, but the optimal duration of these therapies is questionable (14, 64, 65). Moreover, it should be noted that AIs might be administered from 5 to more than 10

**TABLE 4 |** Quality assessment of the studies included in the present systematic review.

| Articles | Domain | | | | | Score |
|---|---|---|---|---|---|---|
| | Random sequence generation | Appropriate randomization | Blinding of participants or personnel | Blinding of outcome assessors | Withdrawals and dropouts | |
| Brufsky et al. (52) | 1 | 1 | 0 | 0 | 1 | 3 |
| Brufsky et al. (48) | 1 | 1 | 0 | 0 | 1 | 3 |
| Brufsky et al. (50) | 1 | 1 | 0 | 0 | 1 | 3 |
| Bundred et al. (24) | 1 | 1 | 0 | 0 | 1 | 3 |
| Eidtmann et al. (47) | 1 | 1 | 0 | 0 | 1 | 3 |
| Coleman et al. (39) | 1 | 1 | 0 | 0 | 1 | 3 |
| Ellis et al. (49) | 1 | 1 | 1 | 1 | 1 | 5 |
| Gnant et al. (34) | 1 | 1 | 1 | 1 | 1 | 5 |
| Gnant et al. (35) | 1 | 1 | 1 | 1 | 1 | 5 |
| Greenspan et al. (38) | 1 | 1 | 1 | 1 | 1 | 5 |
| Lester et al. (41) | 1 | 1 | 0 | 0 | 1 | 3 |
| Lester et al. (42) | 1 | 1 | 0 | 0 | 1 | 3 |
| Livi et al. (29) | 1 | 1 | 1 | 0 | 1 | 4 |
| Llombart et al. (44) | 1 | 1 | 0 | 0 | 1 | 3 |
| Markopoulos et al. (46) | 0 | 0 | 0 | 0 | 1 | 1 |
| Rhee et al. (40) | 1 | 1 | 1 | 1 | 1 | 5 |
| Safra et al. (51) | 1 | 1 | 0 | 0 | 1 | 3 |
| Takahashi et al. (43) | 1 | 1 | 0 | 0 | 1 | 3 |
| Van Poznak et al. (45) | 1 | 1 | 1 | 1 | 1 | 5 |
| Hines et al. (36) | 1 | 1 | 0 | 0 | 1 | 3 |
| Wagner-Johnston et al. (37) | 1 | 1 | 0 | 0 | 1 | 3 |

*Points were awarded as follows: study described as randomized, 1 point; appropriate randomization, 1 point; subjects blinded to intervention, 1 point; evaluator blinded to intervention, 1 point; description of withdrawals and dropouts, 1 point.*

years (66), while studies assessing the long-term effects of denosumab or BPs in BC patients lasted 5-8 years (35, 39). Therefore, data supporting the long-term effects of anti-resorptive drugs on bone health in EBC patients receiving AIs are warranted.

This paper has some limitations which need to be taken into consideration. Firstly, only RCTs were included, thus excluding evidence provided by observational studies. Furthermore, because of statistical and methodologic heterogeneity among studies included, we did not carry out a pairwise or network meta-analysis.

In conclusion, bone health management is a cornerstone in the comprehensive management of patients with EBC receiving adjuvant AIs. Despite the remarkable advancements in understanding the mechanisms underpinning AI-induced bone loss, the optimal therapeutic framework for these patients remains a challenge for physicians.

This systematic review showed that denosumab and zoledronic acid might be considered the most effective anti-resorptive treatment options to improve BMD in patients with EBC on adjuvant AIs. However, robust data concerning the long-term effects of these drugs and their impact on the HRQoL are lacking. Thus, further studies addressing the long-term impact of these drugs are warranted. This could provide insightful evidence to guide clinicians in using tailored and effective treatments for BC survivors, to finally reduce their fracture risk and improve both HRQoL and long-term outcomes.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## AUTHOR CONTRIBUTIONS

Study design and conceptualization: AS and MI. Databases searching: AS. Data screening: AS, LL, and MI. Data extraction: AS, LL, and MI. Data synthesis and interpretation: AS, LL, and MI. Manuscript drafting: AS and LL. Critical revision: KV, SM, NF, and MI. Visualization: ES, CCu, AA, and CCr. Study supervision: AS and MI. Study submission: AS. All authors read and approved the final version of the manuscript.

## ACKNOWLEDGMENTS

The authors would like to thank Alberto Patella, MD for his support in this work.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.829875/full#supplementary-material

## REFERENCES


1. Iacoviello L, Bonaccio M, de Gaetano G, Donati MB. Epidemiology of Breast Cancer, a Paradigm of the "Common Soil" Hypothesis. *Semin Cancer Biol* (2021) 72:4–10. doi: 10.1016/j.semcancer.2020.02.010
2. Lima SM, Kehm RD, Terry MB. Global Breast Cancer Incidence and Mortality Trends by Region, Age-Groups, and Fertility Patterns. *E Clin Med* (2021) 38:100985. doi: 10.1016/j.eclinm.2021.100985
3. de Sire A, Fusco N, Sajjadi E, Lippi L, Cisari C, Invernizzi M. Lymphedema Rehabilitation Using Self-Adaptive Inelastic Compression in Breast Cancer: A Proof-Of-Principle Study. *Appl Sci* (2021) 11(4):1901. doi: 10.3390/app11041901
4. de Sire A, Losco L, Cigna E, Lippi L, Gimigliano F, Gennari A, et al. Three-Dimensional Laser Scanning as a Reliable and Reproducible Diagnostic Tool in Breast Cancer Related Lymphedema Rehabilitation: A Proof-of-Principle Study. *Eur Rev Med Pharmacol Sci* (2020) 24(8):4476–85. doi: 10.26355/eurrev_202004_21030
5. Invernizzi M, de Sire A, Lippi L, Venetis K, Sajjadi E, Gimigliano F, et al. Impact of Rehabilitation on Breast Cancer Related Fatigue: A Pilot Study. *Front Oncol* (2020) 10:556718. doi: 10.3389/fonc.2020.556718
6. de Sire A, Losco L, Cisari C, Gennari A, Boldorini R, Fusco N, et al. Axillary Web Syndrome in Women After Breast Cancer Surgery Referred to an Oncological Rehabilitation Unit: Which Are the Main Risk Factors? A Retrospective Case-Control Study. *Eur Rev Med Pharmacol Sci* (2020) 24 (15):8028–35. doi: 10.26355/eurrev_202008_22486
7. Invernizzi M, Lopez G, Michelotti A, Venetis K, Sajjadi E, De Mattos-Arruda L, et al. Integrating Biological Advances Into the Clinical Management of Breast Cancer Related Lymphedema. *Front Oncol* (2020) 10:422. doi: 10.3389/fonc.2020.00422
8. Invernizzi M, Kim J, Fusco N. Editorial: Quality of Life in Breast Cancer Patients and Survivors. *Front Oncol* (2020) 10:620574. doi: 10.3389/fonc.2020.620574
9. de Sire A, Ferrillo M, Gennari A, Cisari C, Pasqua S, Foglio Bonda PL, et al. Bone Health, Vitamin D Status and Oral Hygiene Screening in Breast Cancer Women Before Starting Osteoporosis Treatment: A Cross-Sectional Study. *J Biol Regul Homeost Agents* (2021) 35(1):397–402. doi: 10.23812/20-686-L
10. Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. *J Clin Oncol* (2014) 32(21):2255–69. doi: 10.1200/JCO.2013.54.2258
11. Diana A, Carlino F, Giunta EF, Franzese E, Guerrera LP, Di Lauro V, et al. Cancer Treatment-Induced Bone Loss (CTIBL): State of the Art and Proper Management in Breast Cancer Patients on Endocrine Therapy. *Curr Treat Options Oncol* (2021) 22(5):45. doi: 10.1007/s11864-021-00835-2
12. Scaturro D, de Sire A, Terrana P, Curci C, Vitagliani F, Falco V, et al. Early Denosumab for the Prevention of Osteoporotic Fractures in Breast Cancer Women Undergoing Aromatase Inhibitors: A Case-Control Retrospective Study. *J Back Musculoskelet Rehabil* (2021) 1–6. doi: 10.3233/BMR-210012
13. Migliaccio S, de Sire A, Marocci C, Fornari R, Paoletta M, Greco EA, et al. Approach in Aromatase Inhibitors - Induced Osteoporosis: Results From an Italian Multicenter Observational Study. *Clin cases Miner Bone Metab* (2018) 15(3):334–9.
14. Hadji P, Coleman RE, Wilson C, Powles TJ, Clézardin P, Aapro M, et al. Adjuvant Bisphosphonates in Early Breast Cancer: Consensus Guidance for Clinical Practice From a European Panel. *Ann Oncol* (2016) 27(3):379–90. doi: 10.1093/annonc/mdv617
15. Kroep JR, Charehbili A, Coleman RE, Aft RL, Hasegawa Y, Winter MC, et al. Effects of Neoadjuvant Chemotherapy With or Without Zoledronic Acid on Pathological Response: A Meta-Analysis of Randomised Trials. *Eur J Cancer* (2016) 54:57–63. doi: 10.1016/j.ejca.2015.10.011
16. Zhao YY, Xue C, Hou X, Liao H, Li S, Zhao HY, et al. Changes of Bone Resorption Marker (NTX) in Chemotherapy Plus Zoledronic Acid Versus Chemotherapy Alone for Nasopharyngeal Cancer Patients With Bone Metastases. *Eur J Cancer* (2011) 47(6):848–53. doi: 10.1016/j.ejca.2010.12.004
17. Hadji P, Ziller M, Maskow C, Albert U, Kalder M. The Influence of Chemotherapy on Bone Mineral Density, Quantitative Ultrasonometry and Bone Turnover in Pre-Menopausal Women With Breast Cancer. *Eur J Cancer* (2009) 45(18):3205–12. doi: 10.1016/j.ejca.2009.09.026
18. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase Inhibitors Versus Tamoxifen in Early Breast Cancer: Patient-Level Meta-Analysis of the Randomised Trials. *Lancet* (2015) 386(10001):1341–52. doi: 10.1016/S0140-6736(15)61074-1
19. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, et al. Primary Breast Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. *Ann Oncol* (2015) 26 Suppl 5:v8–30. doi: 10.1093/annonc/mdv298
20. Hadji P. Cancer Treatment-Induced Bone Loss in Women With Breast Cancer. *Bonekey Rep* (2015) 4:692. doi: 10.1038/bonekey.2015.60
21. Rizzoli R, Body JJ, DeCensi A, Reginster JY, Piscitelli P, Brandi ML, et al. Guidance for the Prevention of Bone Loss and Fractures in Postmenopausal Women Treated With Aromatase Inhibitors for Breast Cancer: An ESCEO Position Paper. *Osteoporos Int* (2012) 23(11):2567–76. doi: 10.1007/s00198-011-1870-0
22. Cheung AM, Heisey R, Srighanthan J. Breast Cancer and Osteoporosis. *Curr Opin Endocrinol Diabetes Obes* (2013) 20(6):532–8. doi: 10.1097/01.med.0000436195.10599.dd
23. Paschou SA, Augoulea A, Lambrinoudaki I. Bone Health Care in Women With Breast Cancer. *Hormones (Athens)* (2020) 19(2):171–8. doi: 10.1007/s42000-019-00164-y
24. Bundred NJ, Campbell ID, Davidson N, DeBoer RH, Eidtmann H, Monnier A, et al. Effective Inhibition of Aromatase Inhibitor-Associated Bone Loss by Zoledronic Acid in Postmenopausal Women With Early Breast Cancer Receiving Adjuvant Letrozole: ZO-FAST Study Results. *Cancer* (2008) 112 (5):1001–10. doi: 10.1002/cncr.23259
25. Gnant M, Mlineritsch B, Schippinger W, Luschin-Ebengreuth G, Pöstlberger S, Menzel C, et al. Endocrine Therapy Plus Zoledronic Acid in Premenopausal Breast Cancer. *N Engl J Med* (2009) 12;360(7):679–91. doi: 10.1056/NEJMoa0806285
26. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for Prevention of Fractures in Postmenopausal Women With Osteoporosis. *N Engl J Med* (2009) 361(8):756–65. doi: 10.1056/NEJMoa0809493
27. Lipton A, Smith MR, Ellis GK, Goessl C. Treatment-Induced Bone Loss and Fractures in Cancer Patients Undergoing Hormone Ablation Therapy: Efficacy and Safety of Denosumab. *Clin Med Insights Oncol* (2012) 6:287–303. doi: 10.4137/CMO.S8511
28. Lipton A, Fizazi K, Stopeck AT, Henry DH, Brown JE, Yardley DA, et al. Superiority of Denosumab to Zoledronic Acid for Prevention of Skeletal-Related Events: A Combined Analysis of 3 Pivotal, Randomised, Phase 3 Trials. *Eur J Cancer* (2012) 48(16):3082–92. doi: 10.1016/j.ejca.2012.08.002
29. Livi L, Scotti V, Desideri I, Saieva C, Cecchini S, Francolini G, et al. Phase 2 Placebo-Controlled, Single-Blind Trial to Evaluate the Impact of Oral Ibandronate on Bone Mineral Density in Osteopenic Breast Cancer Patients Receiving Adjuvant Aromatase Inhibitors: 5-Year Results of the Single-Centre BONADIUV Trial. *Eur J Cancer* (2019) 108:100–10. doi: 10.1016/j.ejca.2018.12.005
30. Yan T, Yin W, Zhou Q, Zhou L, Jiang Y, Du Y, et al. The Efficacy of Zoledronic Acid in Breast Cancer Adjuvant Therapy: A Meta-Analysis of Randomised Controlled Trials. *Eur J Cancer* (2012) 48(2):187–95. doi: 10.1016/j.ejca.2011.10.021
31. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ* (2021) 372:n71. doi: 10.1136/bmj.n71
32. Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a Knowledge Representation for Clinical Questions. *AMIA Annu Symp Proc* (2006) 2006:359–63.
33. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? *Control Clin Trials* (1996) 17(1):1–12. doi: 10.1016/0197-2456(95)00134-4
34. Gnant M, Pfeiler G, Dubsky PC, Hubalek M, Greil R, Jakesz R, et al. Adjuvant Denosumab in Breast Cancer (ABCSG-18): A Multicentre, Randomised, Double-Blind, Placebo-Controlled Trial. *Lancet* (2015) 386(9992):433–43. doi: 10.1016/S0140-6736(15)60995-3

35. Gnant M, Pfeiler G, Steger GG, Egle D, Greil R, Fitzal F, et al. Adjuvant Denosumab in Postmenopausal Patients With Hormone Receptor-Positive Breast Cancer (ABCSG-18): Disease-Free Survival Results From a Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. *Lancet Oncol* (2019) 20(3):339–51. doi: 10.1016/S1470-2045(18)30862-3
36. Hines SL, Mincey B, Dentchev T, Sloan JA, Perez EA, Johnson DB, et al. Immediate Versus Delayed Zoledronic Acid for Prevention of Bone Loss in Postmenopausal Women With Breast Cancer Starting Letrozole After Tamoxifen-N03CC. *Breast Cancer Res Treat* (2009) 117(3):603–9. doi: 10.1007/s10549-009-0332-2
37. Wagner-Johnston ND, Sloan JA, Liu H, Kearns AE, Hines SL, Puttabasavaiah S, et al. 5-Year Follow-Up of a Randomized Controlled Trial of Immediate Versus Delayed Zoledronic Acid for the Prevention of Bone Loss in Postmenopausal Women With Breast Cancer Starting Letrozole After Tamoxifen: N03CC (Alliance) Trial. *Cancer* (2015) 121(15):2537–43. doi: 10.1002/cncr.29327
38. Greenspan SL, Vujevich KT, Brufsky A, Lembersky BC, van Londen GJ, Jankowitz RC, et al. Prevention of Bone Loss With Risedronate in Breast Cancer Survivors: A Randomized, Controlled Clinical Trial. *Osteoporos Int* (2015) 26(6):1857–64. doi: 10.1007/s00198-015-3100-7
39. Coleman R, de Boer R, Eidtmann H, Llombart A, Davidson N, Neven P, et al. Zoledronic Acid (Zoledronate) for Postmenopausal Women With Early Breast Cancer Receiving Adjuvant Letrozole (ZO-FAST Study): Final 60-Month Results. *Ann Oncol* (2013) 24(2):398–405. doi: 10.1093/annonc/mds277
40. Rhee Y, Song K, Park S, Park HS, Lim SK, Park BW. Efficacy of a Combined Alendronate and Calcitriol Agent (Maxmarvil®) in Korean Postmenopausal Women With Early Breast Cancer Receiving Aromatase Inhibitor: A Double-Blind, Randomized, Placebo-Controlled Study. *Endocr J* (2013) 60(2):167–72. doi: 10.1507/endocrj.ej12-0283
41. Lester JE, Dodwell D, Purohit OP, Gutcher SA, Ellis SP, Thorpe R, et al. Prevention of Anastrozole-Induced Bone Loss With Monthly Oral Ibandronate During Adjuvant Aromatase Inhibitor Therapy for Breast Cancer. *Clin Cancer Res* (2008) 14(19):6336–42. doi: 10.1158/1078-0432.CCR-07-5101
42. Lester JE, Dodwell D, Brown JE, Purohit OP, Gutcher SA, Ellis SP, et al. Prevention of Anastrozole Induced Bone Loss With Monthly Oral Ibandronate: Final 5 Year Results From the ARIBON Trial. *J Bone Oncol* (2012) 1(2):57–62. doi: 10.1016/j.jbo.2012.06.002
43. Takahashi S, Iwase T, Kohno N, Ishikawa T, Taguchi T, Takahashi M, et al. Efficacy of Zoledronic Acid in Postmenopausal Japanese Women With Early Breast Cancer Receiving Adjuvant Letrozole: 12-Month Results. *Breast Cancer Res Treat* (2012) 133(2):685–93. doi: 10.1007/s10549-012-1973-0
44. Llombart A, Frassoldati A, Paija O, Sleeboom HP, Jerusalem G, Mebis J, et al. Immediate Administration of Zoledronic Acid Reduces Aromatase Inhibitor-Associated Bone Loss in Postmenopausal Women With Early Breast Cancer: 12-Month Analysis of the E-ZO-FAST Trial. *Clin Breast Cancer* (2012) 12(1):40–8. doi: 10.1016/j.clbc.2011.08.002
45. Van Poznak C, Hannon RA, Mackey JR, Campone M, Apffelstaedt JP, Clack G, et al. Prevention of Aromatase Inhibitor-Induced Bone Loss Using Risedronate: The SABRE Trial. *J Clin Oncol* (2010) 28(6):967–75. doi: 10.1200/JCO.2009.24.5902
46. Markopoulos C, Tzoracoleftherakis E, Polychronis A, Venizelos B, Dafni U, Xepapadakis G, et al. Management of Anastrozole-Induced Bone Loss in Breast Cancer Patients With Oral Risedronate: Results From the ARBI Prospective Clinical Trial. *Breast Cancer Res* (2010) 12(2):R24. doi: 10.1186/bcr2565
47. Eidtmann H, de Boer R, Bundred N, Llombart-Cussac A, Davidson N, Neven P, et al. Efficacy of Zoledronic Acid in Postmenopausal Women With Early Breast Cancer Receiving Adjuvant Letrozole: 36-Month Results of the ZO-FAST Study. *Ann Oncol* (2010) 21(11):2188–94. doi: 10.1093/annonc/mdq217
48. Brufsky AM, Bosserman LD, Caradonna RR, Haley BB, Jones CM, Moore HC, et al. Zoledronic Acid Effectively Prevents Aromatase Inhibitor-Associated Bone Loss in Postmenopausal Women With Early Breast Cancer Receiving Adjuvant Letrozole: Z-FAST Study 36-Month Follow-Up Results. *Clin Breast Cancer* (2009) 9(2):77–85. doi: 10.3816/CBC.2009.n.015
49. Ellis GK, Bone HG, Chlebowski R, Paul D, Spadafora S, Smith J, et al. Randomized Trial of Denosumab in Patients Receiving Adjuvant Aromatase Inhibitors for Nonmetastatic Breast Cancer. *J Clin Oncol* (2008) 26(30):4875–82. doi: 10.1200/JCO.2008.16.3832
50. Brufsky AM, Harker WG, Beck JT, Bosserman L, Vogel C, Seidler C, et al. Final 5-Year Results of Z-FAST Trial: Adjuvant Zoledronic Acid Maintains Bone Mass in Postmenopausal Breast Cancer Patients Receiving Letrozole. *Cancer* (2012) 118(5):1192–201. doi: 10.1002/cncr.26313
51. Safra T, Bernstein-Molho R, Greenberg J, Pelles-Avraham S, Stephansky I, Sarid D, et al. The Protective Effect of Zoledronic Acid on Bone Loss in Postmenopausal Women With Early Breast Cancer Treated With Sequential Tamoxifen and Letrozole: A Prospective, Randomized, Phase II Trial. *Oncology* (2011) 81(5-6):298–305. doi: 10.1159/000334456
52. Brufsky A, Bundred N, Coleman R, Lambert-Falls R, Mena R, Hadji P, et al. Z-FAST and ZO-FAST Study Groups. Integrated Analysis of Zoledronic Acid for Prevention of Aromatase Inhibitor-Associated Bone Loss in Postmenopausal Women With Early Breast Cancer Receiving Adjuvant Letrozole. *Oncologist* (2008) 13(5):503–14. doi: 10.1634/theoncologist.2007-0206
53. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? *Control Clin Trials* (1996) 17(1):1–12. doi: 10.1016/0197-2456(95)00134-4
54. Kelly RR, McDonald LT, Jensen NR, Sidles SJ, LaRue AC. Impacts of Psychological Stress on Osteoporosis: Clinical Implications and Treatment Interactions. *Front Psychiatry* (2019) 10:200. doi: 10.3389/fpsyt.2019.00200
55. Moretti A, de Sire A, Curci C, Toro G, Gimigliano F, Iolascon G. Effectiveness of Denosumab on Back Pain-Related Disability and Quality-of-Life in Patients With Vertebral Fragility Fractures. *Curr Med Res Opin* (2019) 35(1):151–5. doi: 10.1080/03007995.2018.1545636
56. Invernizzi M, de Sire A, Venetis K, Cigna E, Carda S, Borg M, et al. Quality of Life Interventions in Breast Cancer Survivors: State of the Art in Targeted Rehabilitation Strategies. *Anticancer Agents Med Chem* (2021). doi: 10.2174/1871520621666210609095602
57. Coleman R, Finkelstein DM, Barrios C, Martin M, Iwata H, Hegg R, et al. Adjuvant Denosumab in Early Breast Cancer (D-CARE): An International, Multicentre, Randomised, Controlled, Phase 3 Trial. *Lancet Oncol* (2020) 21(1):60–72. doi: 10.1016/S1470-2045(19)30687-4
58. von Minckwitz G, Möbus V, Schneeweiss A, Huober J, Thomssen C, Untch M, et al. German Adjuvant Intergroup Node-Positive Study: A Phase III Trial to Compare Oral Ibandronate Versus Observation in Patients With High-Risk Early Breast Cancer. *J Clin Oncol* (2013) 31(28):3531–9. doi: 10.1200/JCO.2012.47.2167
59. Coleman RE, Collinson M, Gregory W, Marshall H, Bell R, Dodwell D, et al. Benefits and Risks of Adjuvant Treatment With Zoledronic Acid in Stage II/III Breast Cancer. 10 Years Follow-Up of the AZURE Randomized Clinical Trial (BIG 01/04). *J Bone Oncol* (2018) 13:123–35. doi: 10.1016/j.jbo.2018.09.008
60. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant Bisphosphonate Treatment in Early Breast Cancer: Meta-Analyses of Individual Patient Data From Randomised Trials. *Lancet* (2015) 386(10001):1353–61. doi: 10.1016/S0140-6736(15)60908-4
61. Hadji P, Aapro MS, Body JJ, Gnant M, Brandi ML, Reginster JY, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in Postmenopausal Women With Hormone Sensitive Breast Cancer: Joint Position Statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. *J Bone Oncol* (2017) 7:1–12. doi: 10.1016/j.jbo.2017.03.001
62. Dhesy-Thind S, Fletcher GG, Blanchette PS, Clemons MJ, Dillmon MS, Frank ES, et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* (2017) 20;35(18):2062–81. doi: 10.1200/JCO.2016.70.7257
63. National Guideline Alliance (UK). *Early and Locally Advanced Breast Cancer: Diagnosis and Management*. London: National Institute for Health and Care Excellence (UK (2018).
64. Coleman R, Hadji P, Body JJ, Santini D, Chow E, Terpos E, et al. Electronic Address: Clinicalguidelines@Esmo.Org. Bone Health in Cancer: ESMO Clinical Practice Guidelines. *Ann Oncol* (2020) 31(12):1650–63. doi: 10.1016/j.annonc.2020.07.019

65. Dhesy-Thind S, Fletcher GG, Blanchette PS, Clemons MJ, Dillmon MS, Frank ES, et al. Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* (2017) 35 (18):2062–81. doi: 10.1200/JCO.2016.70.7257
66. Goss PE, Ingle JN, Pritchard KI, Robert NJ, Muss H, Gralow J, et al. Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. *N Engl J Med* (2016) 375 (3):209–19. doi: 10.1056/NEJMoa1604700

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

STUDY PROTOCOL
published: 01 March 2022
doi: 10.3389/fonc.2022.850564

# Effect of Supervised Resistance Training on Arm Volume, Quality of Life and Physical Perfomance Among Women at High Risk for Breast Cancer-Related Lymphedema: A Study Protocol for a Randomized Controlled Trial (STRONG-B)

*Karol Ramírez-Parada[1]*, Maria Lopez-Garzon[2,3,4]*, Cesar Sanchez-Rojel[5], Militza Petric-Guajardo[6,7], Margarita Alfaro-Barra[8], Rodrigo Fernández-Verdejo[9], Alvaro Reyes-Ponce[10], Gina Merino-Pereira[11,12,13] and Irene Cantarero-Villanueva[2,3,4,14]*

*[1] Carrera de Kinesiología, Departamento Ciencias de la Salud, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile, [2] 'Cuídate' From Biomedical Group (BIO277), Instituto de Investigación Biosanitaria (ibs.GRANADA), Granada, Spain, [3] Department of Physical Therapy, Faculty of Health Sciences, University of Granada, Granada, Spain, [4] Unit of Excellence on Exercise and Health (UCEES), University of Granada, Granada, Spain, [5] Departamento de Hematología-Oncología, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile, [6] Department of Surgery Dr Sótero del Río Hospital, Santiago, Chile, [7] Department of Surgery Davila Clinic, Santiago, Chile, [8] Centro de Cáncer, Red de Salud U- Christus, Pontificia Universidad Católica de Chile, Santiago, Chile, [9] Laboratorio de Fisiología del Ejercicio y Metabolismo (LABFEM), Escuela de Kinesiología, Facultad de Medicina, Universidad Finis Terrae, Santiago, Chile, [10] Escuela de Kinesiología, Facultad de Ciencias de la Rehabilitación, Universidad Andrés Bello, Viña del Mar, Chile, [11] Departamento Manejo Integral del Cáncer y Otros Tumores, Subsecretaria de Salud Pública, Ministerio de Salud de Chile, Santiago, Chile, [12] Escuela de Medicina, Facultad de Ciencias, Universidad Mayor, Santiago, Chile, [13] Instituto de Investigación y Postgrado, Facultad de Ciencias de la Salud, Universidad Central de Chile, Santiago, Chile, [14] Sport and Health Research Center (iMUDS), Granada, Spain*

**Objectives:** To determine the preventive effects of supervised resistance training on arms volume, quality of life, physical performance, and handgrip strength in Chilean women at high risk for breast cancer-related lymphedema (BCRL) undergoing chemotherapy.

**Design:** Randomized control trial.

**Participants:** One hundred and six women at high risk for breast cancer-related lymphedema aged 18 to 70 years.

**Interventions:** Participants will be randomized into two groups: [a] intervention, who will receive 12 weeks of supervised resistance training (STRONG-B) during adjuvant chemotherapy; and [b] control, who will receive education to promote lymphatic and venous return, maintain range of motion, and promote physical activity.

**Main Outcome Measures:** The primary outcome will be arms volume measured with an optoelectric device (perometer NT1000). Secondary outcomes will be quality of life, handgrip strength, and physical performance. Primary and secondary outcomes will be measured at baseline, just after the intervention, and 3 and 6 months after. Statistical

OPEN ACCESS

**Edited by:**
*Julio de la Torre, Comillas Pontifical University, Spain*

**Reviewed by:**
*Marco Invernizzi, University of Eastern Piedmont, Italy*
*Alessandro de Sire, University of Magna Graecia, Italy*

***Correspondence:**
*Karol Ramírez-Parada*
*kramirezp@uc.cl*
*Maria Lopez-Garzon*
*maloga@go.ugr.es*

**Specialty section:**
*This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology*

**Received:** *07 January 2022*
**Accepted:** *01 February 2022*
**Published:** *01 March 2022*

**Citation:**
*Ramírez-Parada K, Lopez-Garzon M, Sánchez-Rojel C, Petric-Guajardo M, Alfaro-Barra M, Fernandez-Verdejo R, Reyes-Ponce A, Merino-Pereira G and Cantarero-Villanueva I (2022) Effect of Supervised Resistance Training on Arm Volume, Quality of Life and Physical Perfomance Among Women at High Risk for Breast Cancer-Related Lymphedema: A Study Protocol for a Randomized Controlled Trial (STRONG-B). Front. Oncol. 12:850564. doi: 10.3389/fonc.2022.850564*

analysis will be performed following intention-to-treat and per-protocol approaches. The treatment effect will be calculated using linear mixed models.

**Discussion:** The STRONG-B will be a tailored supervised resistance training that attempts to prevent or mitigate BCRL in a population that, due to both intrinsic and extrinsic factors, will commonly suffer from BCRL.

**Clinical Trial Registration:** [https://clinicaltrials.gov/ct2/show/NCT04821609], identifier NCT04821609.

**Keywords: breast cancer lymphedema, breast neoplasms, physical therapy specialty, quality of life, resistance training**

## INTRODUCTION

Breast cancer is the leading cause of cancer mortality among women worldwide (1–3). While early detection and better treatment strategies have improved overall survival (4, 5), patients often develop adverse effects such as fatigue, pain, sensory loss, impairments in shoulder range of motion and muscle strength, axillary web syndrome, and lymphedema (6–10). These effects ultimately impair survivors' quality of life and physical performance (11–14).

Among the adverse effects, lymphedema deserves attention because of its chronic nature (15). One-third of breast cancer survivors develop breast cancer-related arm lymphedema (BCRL), 80% of them closely after treatments (16–18). BCRL is an excess accumulation of protein-rich fluid that would otherwise drain *via* the lymphatic system, leading to regional swelling in one or both arms after breast cancer (19, 20). BCRL has multifactorial causes, influenced by treatment strategies and the patient's ability to form collateral lymphatic pathways post-injury (20, 21). Major risk factors for BCRL are obesity (body mass index ≥30 kg/m$^2$), extensive breast and axillary lymph node surgery, radiotherapy in lymph node basin, and taxane chemotherapy (10, 14, 20, 22). Clinically, BCRL is characterized by increased arm volume associated with pain, heaviness, tightness, and a decreased range of motion, thus impacting the quality of life (23, 24).

The treatment for BCRL focuses on volume control through physiotherapy and compression garments (25–27), which represents a high economic burden for patients and the health care system (28). Identifying strategies to prevent BCRL in individuals at high risk, and to improve quality of life of patients is necessary (27).

Historically, there has been objection to promoting physical exercise or weight lifting to breast cancer survivors (29). Nevertheless, this is currently regarded as safe (30). Indeed, there has been an emerging interest in physical exercise (aerobic and resistance) as a safe and effective complementary intervention to prevent or diminish the adverse effects related to breast cancer treatments (31–33).

Exercise increases cardiac output and arterial blood pressure, thus promoting capillary filtration and the entry of fluid and proteins into lymphatic capillaries (34). Exercise also increases lymph propulsion through lymphatic vessels through extrinsic and intrinsic mechanisms, e.g. skeletal muscle pump, respiratory pump, and the pulse of blood vessels near to lymphatic system (34–36). Indeed, lymphatic clearance rates during the initial 15 min of exercise are 5-fold higher than at rest, and remain elevated during exercise (~2.5-fold) (37). Further, physical activity has been shown to improve the quality of life in women with breast cancer (38–40). As mentioned above, physical activity has been also used safely to treat BCRL in survivors (33).

Recent systematic reviews suggest that resistance exercise is a potentially effective strategy to prevent BCRL in women (30, 41); however, few studies included women exclusively at high risk of BCRL (33, 42). The results reported may thus not apply to women at high risk of BCRL. In addition, the studies including women at high risk of BCRL used resistance training with light loads (33). Light training load has a small effect on muscle strength and morphological adaptations, and minor improvements in physical performance and quality of life (41). In contrast, acute (43) and cumulative (42) heavy-load resistance exercises improved the quality of life, muscle strength, and physical performance without increasing risk for BCRL.

Therefore, this study will aim to determine the preventive effects of supervised resistance training on arms volume, quality of life, physical performance, and handgrip strength in women undergoing adjuvant chemotherapy with a high risk of BCRL.

## METHODS

### Study Design

This manuscript is a study protocol for a two-arm, randomized controlled trial (STRONG-B). The protocol adheres to the Recommendations for Interventional Trials (SPIRIT) guidelines (44) and the CONSORT statement (45) (**Figures 1**, **2**, respectively). The STRONG-B trial has been registered in Clinicaltrial.gov (code NCT04821609).

The study population will be participants with breast cancer recruited from Complejo Asistencial Dr. Sótero Del Río by medical referral. Recruitment will take place in two distinct phases. First, a nurse will identify potential participants, and the health and medical records of volunteers will be further analyzed in a multidisciplinary committee, including medical oncologists, surgeons, and radio-oncologists. In the second phase, each volunteer's eligibility will be

| | STUDY PERIOD | | | | |
|---|---|---|---|---|---|
| | Enrolment | Allocation | Post-allocation | | |
| TIMEPOINT | $-t_1$ | 0 | $t_1$ | $t_2$ | $t_3$ |
| **ENROLMENT:** | | | | | |
| Eligibility screen | X | | | | |
| Informed consent | X | | | | |
| Allocation | | X | | | |
| **INTERVENTIONS:** | | | | | |
| *Intervention group: STRONG-B* | | | ← | — | → |
| *Control group* | | | ← | — | → |
| **ASSESSMENTS:** | | | | | |
| *Sociodemographic data* | X | | | | |
| *Anthropometric data* | X | | | | |
| *Clinical data* | X | | | | |
| *Quality of life* | X | | X | X | X |
| *Arms volume* | X | | X | X | X |
| *Physical functioning* | X | | X | X | X |
| *Handgrip strength* | X | | X | X | X |
| *Safety* | | | X | | |
| *Recruitment-acceptance ratio* | X | | | | |
| *Adherence* | | | X | | |

**FIGURE 1** | Schedule of enrolment, interventions, and assessments according to SPIRIT diagram.

confirmed by an oncologist during medical consultation. The same nurse of the first recruitment phase will then explain to each potential volunteer the purpose of the study and perform the informed consent process. Reasons for withdrawal from the study will be recorded.

## Eligibility Criteria

The following inclusion criteria will be applied: [a] women between 18 and 70 years old; [b] diagnosis of primary breast carcinoma with histological confirmation; [c] total or partial mastectomy with axillary node dissection; [d] sentinel node biopsy with positive axillary web syndrome (defined as cord in the subcutaneous tissue from the axilla into the ipsilateral upper arm); [e] sentinel node biopsy along with a body mass index between 30.0 and 39.9 kg/m$^2$; [f] indication of adjuvant chemotherapy; and [g] participants able to understand and respond to simple instructions. The exclusion criteria will be: [a] >200 ml of difference in volume between arms; [b] antineoplastic treatment (chemotherapy, radiation therapy, or hormone therapy) before the current medical diagnosis; [c] stage IV breast cancer; [d] medical contraindication for exercise; [e] self-reported physical activity equivalent to the recent American College of Sports Medicine Physical Exercise Recommendation Guidelines for Patients and Cancer Survivors: 150 min/week of moderate aerobic exercise, or 75 min/week of vigorous aerobic exercise, and resistance training exercises at least two days per week; [f] body mass index <18.5 kg/m$^2$ (indicative of malnutrition) or >40 kg/m$^2$ (indicative of high cardiovascular risk); and [g] pregnancy.

## Intervention

STRONG-B is an exercise training intervention specifically developed for patients with breast cancer (46), which follows the

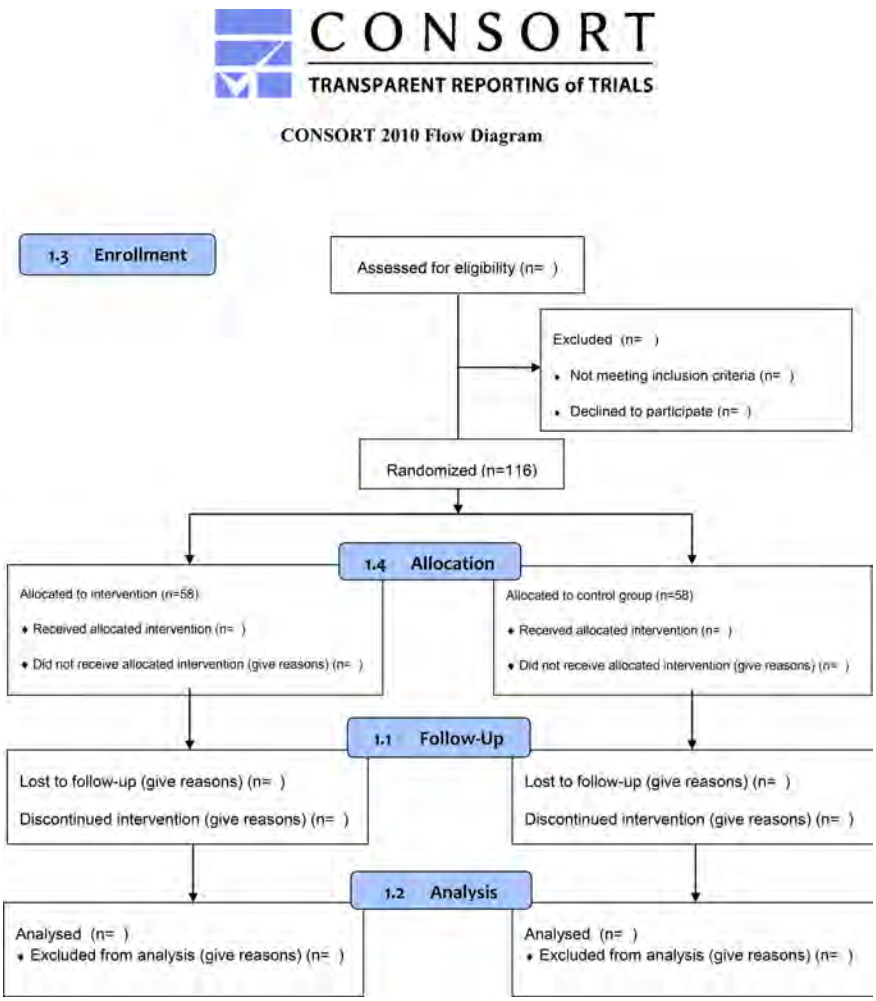



**FIGURE 2** | The proposed CONSORT diagram of enrolment, allocation, follow-up, and analysis through the study for each arm.

guidelines of the American College of Sports Medicine with the specification for the frequency, intensity, time, and type of exercise prescription (31).

The training sessions include ten moderate-intensity resistance exercises for the upper (shoulder press, chest press, lateral pulldown, biceps curls, triceps extension) and lower limbs (squat, calf raise, leg press, leg extension, and leg curl). Each session lasts ~40 minutes and will be conducted twice a week for 12 consecutive weeks. Sessions will be supervised and guided by experienced physiotherapists, and conducted in groups of up to 3 participants.

The training will begin the week after the first chemotherapy session and will be conducted concomitantly with the regular treatment of each patient. Note that STRONG-B will never replace or interfere with the standard care. Each session will include a warm-up (5 minutes), followed by resistance training (30 minutes), and ending with a cooldown (5 minutes).

Resistance exercises will be performed at the maximum range of motion, using resistance machines or free weights as required. Rating of perceived exertion will be measured using a 0–10-point OMNI-Resistance Exercise Scale (minimal effort = 0; maximum effort = 10) to control perceived exercise intensity (47, 48).

During the first week, patients will perform two sets of 10 repetitions of each exercise either without resistance or with the lowest resistance available for a rating of perceived exertion of 2–4 ("easy" to "somewhat easy"). After this week, provided that no adverse events or symptoms are reported, resistance will be added so that each patient can perform three sets of 12 maximal repetitions (12-Repetition maximum) of each exercise with a rating of perceived exertion of 4-6 ("somewhat easy" to "somewhat hard") (47, 48).

Progression will be supervised considering the patient's symptoms (49). When patients can complete three consecutive sessions with the last volume and intensity, the load will be increased 5% to 10%. During the 12th week, the number of steps per day will be recorded using a smart bracelet [Huawei Band 4 (50)] as a surrogate of aerobic physical activity.

## Control Group

Patients in the control group will be referred to an early and prospective physical therapy program, as previously described (51). Therein, they will be evaluated and educated, but this program will not include the STRONG-B training. In the first session (before surgery), patients will receive oral and written education. Education will consist of care advice and eight exercises (**Supplementary Data**) to promote lymphatic and venous return and to maintain arm range of motion. We will recommend patients to perform these exercises in 3 sets of 10 repetitions, 2-3 times a day, for 3 months after surgery. Patients will be also educated to encourage aerobic physical activity. Physical exercise will be evaluated and supervised every three months after surgery, and educational information will be reminded. During the 12th week, the number of steps per day will be recorded using a smart bracelet [Huawei Band 4 (50)] as a surrogate of aerobic physical activity.

# OUTCOMES

## Main Outcome

Arm lymphedema will be assessed using a Perometer (NT 1000, Wuppertal), an optoelectrical imaging device that measures limb volume (52). The perometer is a valid and reliable tool [interclass correlation coefficient test-retest of 0.99 (52)]. The volume is expressed in milliliters and percentage relative to the contralateral arm. A difference in volume between arms of 200 mL or higher and a 10% difference between arms indicate lymphedema (12).

## Secondary Outcomes

Quality of life will be assessed using two questionnaires: [a] the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 v.3.0 [EORTC QLQ-C30; test/retest reliability between 0.82 and 0.91 (53)]; and [b] the European Organization for Research and Treatment of Breast Cancer-Specific Quality of Life Questionnaire BR23 [EORTC QLQ-BR23; Cronbach's $\alpha$ between 0.46 and 0.94 (54)]. These questionnaires had been validated in the Spanish language and Chilean population (55).

Handgrip strength will be measured with a Hydraulic Hand Dynamometer (Jamar, United Kingdom). Patients will be asked to grip and squeeze the dynamometer as hard as possible. The maneuver will be conducted three times, with 1-min rest between attempts. Both hands (with surgery, without surgery) will be measured and compared. Results will be expressed in kilograms. Intra-instrument reliability and concurrent validity were tested using certified standard weights (r = 1.00), while inter-instrument reliability was good, between 0.80 and 0.83 (56). Further, there are reference values for a healthy Chilean population (57, 58).

Physical performance and mobility will be assessed with the 6-minute walk test (59). The test has been validated in patients with cancer and shows good reliability [intraclass correlation coefficient for test/retest was r=0.93 (60)]. Participants will be instructed to walk between two marks set 30 m apart as many times as possible over 6 min. The greater the distance covered, the greater mobility and general performance (59). Results will be expressed in meters walked.

## Sociodemographic and Clinical Data

Demographic data will include age, sex, and educational level. Anthropometric data will include weight, height, and body mass index. Clinical data will include disease stage, scheduled treatment, medical history, and current medication. Clinical data will be extracted from the patients' electronic medical files by one study coordinator not blinded to patient allocation.

## Safety and Feasibility

The safety of the intervention will be assessed every week, tracking and monitoring adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (61). Researchers will meet weekly to review and discuss adverse events. All serious adverse events will be immediately reported to both ethics committees and will be reported in the results.

The number of patients who meet the eligibility criteria, the number of patients who agree or not participate, and the number of patients who withdraw from the study will be recorded and reported. Adherence will be calculated considering the number of patients who participated in all sessions and the number of patients who assisted to scheduled assessments.

## Sample Size

The sample size was determined using G*Power version 3.1.9.2, considering the arm volume as the primary outcome. A confidence level of 95%, statistical power of 90%, and a two-sided alpha of 5% were considered in the analysis. An effect size of 0.70 (d) has been chosen to detect differences in the arm volume in patients with BC undergoing chemotherapy; hence, 44 participants will be needed per group. Considering a dropout rate of 20%, 106 patients will be included in the study.

## Randomization

Patients will be randomly allocated (1:1 ratio) in two concealed numerical lists using the software Sealed Envelope™. The software generates different codes for each patient, which then identifies the group linked to the code. The code will be printed and placed in a dark closed envelope, which will be delivered to patients after baseline assessments. A blinded external researcher will perform the process. The allocation will be then reported to the nurse, who will subsequently inform each participant of the assigned group (intervention or control).

## Study Assessments

**Figure 3** outlines the schedule for study outcome assessments. Assessments will be scheduled upfront, and patients will be regularly reminded *via* phone or email. Outcomes will be measured at four-time points: [t0] at baseline (up to 7 days before chemotherapy); [t1] after intervention (up to 5 days after the intervention ended); [t2] at three months of follow-up; and [t3] at six months of follow-up. Assessments will be made by an experienced researcher blinded to the allocation of patients.

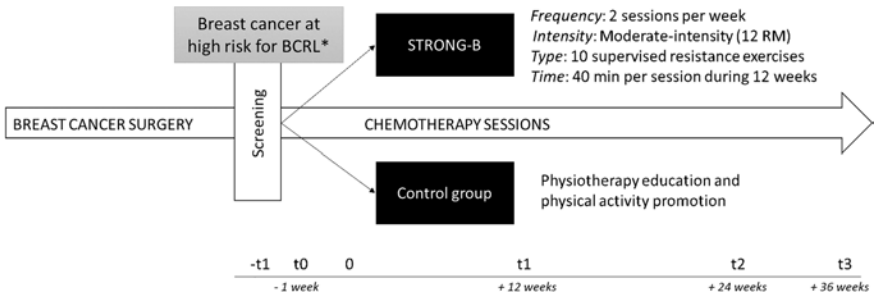



**FIGURE 3** | Study design. *Breast cancer at high risk for breast cancer-related lymphedema (BCRL) has been established as having had: [a] total or partial mastectomy with axillary node dissection; [2] sentinel node biopsy with positive axillary web syndrome; or [3] sentinel node biopsy along with a body mass index between 30.0 and 39.9; F, frequency; I, intensity; T, type; T, time.

## Data Management

Two researchers will manage data using predesigned data collection forms in Excel version 2016 (Microsoft Corporation, Redmond, WA, USA). Data will be regularly revised to ensure data quality. Patients will be identified by codes to ensure anonymity, and only the authors involved in the trial will have access to patients' full identification details.

## Statistical Analyses

Analyses will be performed by a statistician blinded to the allocation of patients. Intention-to-treat and per-protocol approaches will be used. Normality assumption will be tested using the Shapiro-Wilk test. If the normality assumption is met, data will be presented using means and standard deviations. Otherwise, median and interquartile ranges will be reported. To assess the effect of the intervention, a multivariate linear regression model with repeated measurements will be adjusted. The model will include arm volume, quality of life, physical performance, and handgrip strength as response variables. Group (intervention, control), time (t0, t1, t2, t3), and the group×time interaction will be included as explanatory variables, adjusted for co-variables if required. The intervention's effect will be also described by computing the effect size and 95% confidence limits. The following qualitative descriptors will be used: trivial <0.20, small 0.20-0.50, moderate 0.50-0.80, and large >0.80 (62). Significance will be set at $p<0.05$. Statistical analyses will be performed with STATA 15.1.

# DISCUSSION

STRONG-B is a supervised resistance training intervention developed specifically for preventive BCRL in patients with breast cancer at high risk of BCRL. The training will be performed after breast cancer surgery and concomitantly with adjuvant chemotherapy. Considering the impact of cancer and the consequences of the treatments (6–14), the main objective will be to analyze the preventive effects of STRONG-B on arm volume, quality of life, physical performance, and handgrip strength. The feasibility, adherence, and security of the training will be also analyzed. STRONG-B is thus proposed as a tailored resistance training intervention supervised by experienced physiotherapists with multiple potential benefits for patients with breast cancer.

The economic burden of BCRL is high for patients and the health care system (28, 63–65). Three weeks of lymphatic decongestive treatment by a physiotherapist and follow-up require on average USD 2,648 per patient. Additionally, the required compression stockings cost on average USD 937 per patient (28). Finally, there are other non-medical costs such as transportation and loss of productivity due to morbidity and mortality. Together, these data highlight the relevance of developing strategies to prevent BCRL. Physical exercise may represent a plausible strategy (41, 66). If the STRONG-B training is successful, it would be easy to implement in usual care. Since resistance training is safe and well-tolerated in patients with breast cancer, the training may even be used as a primary prevention strategy against lymphedema and deterioration of quality of life.

The interplay and chronology between the factors leading to lymphedema are not well understood (67). Inflammation, adipose tissue remodeling, skin fibrosis, and deterioration of lymphatic vessels are known to be involved (67). Endolymphatic pressure increases immediately after a node resection, leading to irreversible histological changes in collecting lymphatic vessels (68). This process occurs even before the onset of BCRL and involves modifications in endothelial cells and basal membranes and the proliferation of collagen fibers. Interventions at these early stages seem thus essential. Notably, several studies have shown that lymph flow and shear stress are required for valve maintenance (69). Physical exercise can be used for that purpose. Complementing exercises with methods that detect small changes in arm volume [e.g. perometer and three-dimensional laser scanning (52, 70, 71)] will be helpful.

In addition, STRONG-B may have beneficial effects beyond BCRL in women with breast cancer. Long-lasting and high physical activity levels during cancer treatments have been shown to increase chemotherapy completion rate and reduce adverse effects such as fatigue, cardiotoxicity, and cognitive impairments (31, 72–74). This highlights the relevance and impact of chronic exercise interventions in individuals with cancer.

The protocol has certain limitations though. First, aerobic training will not be included, but aerobic physical activity will be encouraged and measured by bracelets in both groups. Second, implementing the training in small groups of patients may delay recruitment but seems safer in the current context of the COVID-19 pandemic. Implementing rehabilitation through telemedicine may

also be useful and complement interventions in the future (75, 76). Third, patients undergoing chemotherapy may feel fatigue or discomfort, thus reducing adherence (77); to prevent this issue, STRONG-B was designed considering the preferences of breast cancer survivors (46). Finally, due to the nature of the intervention, neither participants nor health care workers will be blinded to the group assigned to each participant (78).

In conclusion, the STRONG-B training is proposed as a tailored supervised resistance training for patients with breast cancer at high risk for BCRL. This study will attempt to prevent or mitigate BCRL in a population that, due to both intrinsic and extrinsic factors, will commonly suffer from BCRL

## ETHICS STATEMENT

The study was approved by the "Comité Ético del Servicio de Salud Metropolitano Sur Oriente" (September 24th, 2020) and the "Comité Ético Científico Ciencias de la Salud UC (200310003, 8 October 2020). All patients will receive written and verbal information before starting the study, and written and oral informed consent will be obtained from all participants in the study.

## AUTHOR CONTRIBUTIONS

Conceptualization: KR-P, CS-R, MP-G, and IC-V. Formal analysis: KR-P, ML-G, and IC-V. Methodology: RF-V and AR-P. Project administration: MA-B. Supervision: CS-R, GM-P, and IC-V. Writing – original draft: KR-P, ML-G, and IC-V. Writing – review & editing: KR-P, ML-G, CS-R, MP-G, MA-B, RF-V, AR-P, GM-P, and IC-V. All authors contributed to the article and approved the submitted version.

## FUNDING

The study is funded by ANID+FONDEF/XVII Concurso Nacional de Proyectos de Investigación y Desarrollo en Salud, Fonis (SA20I0060).

## ACKNOWLEDGMENTS

This work is part of KR-P's doctoral work at the Clinical Medicine and Public Health Doctoral Studies of the University of Granada, Spain.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.850564/full#supplementary-material

## REFERENCES

1. Icaza G, Núñez L, Bugueño H. Descripción Epidemiológica De La Mortalidad Por Cáncer De Mama En Mujeres En Chile. *Rev Med Chile* (2017) 145:106–14. doi: 10.4067/S0034-98872017000100014
2. Caglevic C, Anabalón J, Soza C, Milla E, Gaete F, Carrasco AM, et al. Triple-Negative Breast Cancer: The Reality in Chile and in Latin America. *ecancermedicalscience* (2019) 13:893. doi: 10.3332/ecancer.2019.893
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer J Clin* (2021) 71:209–49. doi: 10.3322/caac.21660
4. Birnbaum J, Gadi VK, Markowitz E, Etzioni R. The Effect of Treatment Advances on the Mortality Results of Breast Cancer Screening Trials: A Microsimulation Model. *Ann Internal Med* (2016) 164:236–43. doi: 10.7326/M15-0754
5. Birnbaum JK, Duggan C, Anderson BO, Etzioni R. Early Detection and Treatment Strategies for Breast Cancer in Low-Income and Upper Middle-Income Countries: A Modelling Study. *Lancet Global Health* (2018) 6:e885–93. doi: 10.1016/S2214-109X(18)30257-2
6. Schmitz KH, Speck RM, Rye S a., DiSipio T, Hayes SC. Prevalence of Breast Cancer Treatment Sequelae Over 6 Years of Follow-Up: The Pulling Through Study. *Cancer* (2012) 118:2217–25. doi: 10.1002/cncr.27474
7. Hidding JT, Beurskens CHG, van der Wees PJ, Van Laarhoven HWM, Nijhuis-van Der Sanden MWG. Treatment Related Impairments in Arm and Shoulder in Patients With Breast Cancer: A Systematic Review. *PLoS One* (2014) 9:e96748. doi: 10.1371/journal.pone.0096748
8. Ramírez-Parada K, Garay-Acevedo D, Mella-Abarca W, Petric-Guajardo M, Sánchez-Rojel C, McNeely ML, et al. Axillary Web Syndrome Among Chilean Women With Breast Cancer: Incidence and Possible Predisposing Factors. *Supportive Care Cancer* (2020) 28:2941–7. doi: 10.1007/s00520-019-05190-5
9. Tao JJ, Visvanathan K, Wolff AC. Long Term Side Effects of Adjuvant Chemotherapy in Patients With Early Breast Cancer. *Breast* (2015) 24:S149–53. doi: 10.1016/j.breast.2015.07.035
10. Helms G, Kühn T, Moser L, Remmel E, Kreienberg R. Shoulder-Arm Morbidity in Patients With Sentinel Node Biopsy and Complete Axillary Dissection - Data From a Prospective Randomised Trial. *Eur J Surg Oncol* (2009) 35:696–701. doi: 10.1016/j.ejso.2008.06.013
11. Thomas-MacLean RL, Hack T, Kwan W, Towers A, Miedema B, Tilley A. Arm Morbidity and Disability After Breast Cancer: New Directions for Care. *Oncol Nurs Forum* (2008) 35:65–71. doi: 10.1188/08.ONF.65-71
12. Cormier JN, Xing Y, Zaniletti I, Askew RL, Stewart BR, Armer JM. Minimal Limb Volume Change has a Significant Impact on Breast Cancer Survivors. *Lymphology* (2009) 42:161–75.
13. Togawa K, Ma H, Smith AW, Neuhouser ML, George SM, Baumgartner KB, et al. Self-Reported Symptoms of Arm Lymphedema and Health-Related Quality of Life Among Female Breast Cancer Survivors. *Sci Rep* (2021) 11:1–13. doi: 10.1038/s41598-021-89055-0
14. Lee TS, Kilbreath ÆSL, Refshauge KM, Herbert ÆRD, Beith JM. Prognosis of the Upper Limb Following Surgery and Radiation for Breast Cancer. *Breast Cancer Res Treat* (2008) 110:19–37. doi: 10.1007/s10549-007-9710-9
15. Sleigh BC, Manna B. Lymphedema. In: *Statpearls*. Treasure Island (FL: StatPearls Publishing (2022). Available at: https://www.ncbi.nlm.nih.gov/books/NBK537239/. Updated 2021 June 4.
16. Disipio T, Rye S, Newman B, Hayes S. Incidence of Unilateral Arm Lymphoedema After Breast Cancer: A Systematic Review and Meta-Analysis. *Lancet Oncol* (2013) 14:500–15. doi: 10.1016/S1470-2045(13)70076-7
17. McDuff SGR, Mina AI, Brunelle CL, Salama L, Warren LEG, Abouegylah M, et al. Timing of Lymphedema After Treatment for Breast Cancer: When are Patients Most at Risk? *Int J Radiat Oncol Biol Phys* (2019) 103:62–70. doi: 10.1016/j.ijrobp.2018.08.036

18. Torgbenu E, Luckett T, Buhagiar MA, Chang S, Phillips JL. Prevalence and Incidence of Cancer Related Lymphedema in Low and Middle-Income Countries : A Systematic Review and Meta- Analysis. *BMC Cancer* (2020) 20:604. doi: 10.21203/rs.3.rs-20782/v1
19. Harwood CA, Mortimer PS. Causes and Clinical Manifestations of Lymphatic Failure. *Clinics Dermatol* (1995) 13:459–71. doi: 10.1016/0738-081X(95)00096-X
20. McLaughlin SA, Brunelle CL, Taghian A. Breast Cancer-Related Lymphedema: Risk Factors, Screening, Management, and the Impact of Locoregional Treatment. *J Clin Oncol* (2020) 38:2341–50. doi: 10.1200/JCO.19.02896
21. Cheville AL, McGarvey CL, Petrek JA, Russo SA, Thiadens SRJ, Taylor ME. The Grading of Lymphedema in Oncology Clinical Trials. *Semin Radiat Oncol* (2003) 13:214–25. doi: 10.1016/S1053-4296(03)00038-9.
22. Bradley BJA, Bellon JR. Quality of Life and Limb : Reducing Lymphedema Risk After Breast Cancer Therapy. *Radiat Oncol Biol* (2019) 106:225–9. doi: 10.1016/j.ijrobp.2019.10.033
23. Shaitelman SF, Cromwell KD, Rasmussen JC, Stout NL, Armer JM, Lasinski BB, et al. Recent Progress in the Treatment and Prevention of Cancer-Related Lymphedema. *CA: A Cancer J Clin* (2015) 65:55–81. doi: 10.3322/caac.21253
24. Jørgensen MG, Toyserkani NM, Hansen FG, Bygum A, Sørensen JA. The Impact of Lymphedema on Health-Related Quality of Life Up to 10 Years After Breast Cancer Treatment. *NPJ Breast Cancer* (2021) 7:70. doi: 10.1038/s41523-021-00276-y
25. Lasinski BB, Thrift KMK, Squire DC, Austin MK, Smith KM, Wanchai A, et al. A Systematic Review of the Evidence for Complete Decongestive Therapy in the Treatment of Lymphedema From 2004 to 2011. *PM R* (2012) 4:580–601. doi: 10.1016/j.pmrj.2012.05.003
26. Moseley AL, Carati CJ, Piller NB. A Systematic Review of Common Conservative Therapies for Arm Lymphoedema Secondary to Breast Cancer Treatment. *Ann Oncol* (2007) 18:639–46. doi: 10.1093/annonc/mdl182
27. Davies C, Levenhagen K, Ryans K, Perdomo M, Gilchrist L. Interventions for Breast Cancer-Related Lymphedema: Clinical Practice Guideline From the Academy of Oncologic Physical Therapy of APTA. *Phys Ther* (2020) 100:1163–79. doi: 10.1093/ptj/pzaa087
28. De Vrieze T, Gebruers N, Nevelsteen I, Tjalma WAA, Thomis S, De Groef A, et al. Breast Cancer-Related Lymphedema and its Treatment: How Big is the Financial Impact? *Supportive Care Cancer* (2021) 29:3801–13. doi: 10.1007/s00520-020-05890-3
29. Harris SR, Niesen-Vertommen SL. Challenging the Myth of Exercise-Induced Lymphedema Following Breast Cancer: A Series of Case Reports. *J Surg Oncol* (2000) 74:95–8. doi: 10.1002/1096-9098(200006)74:2<95::AID-JSO3>3.0.CO;2-Q
30. Hasenoehrl T, Keilani M, Palma S, Crevenna R. Resistance Exercise and Breast Cancer Related Lymphedema–a Systematic Review Update. *Disability Rehabil* (2020) 42:26–35. doi: 10.1080/09638288.2018.1514663
31. Campbell KL, Winters-stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise Guidelines for Cancer Survivors: Consensus Statement From International Multidisciplinary Roundtable. *Med Sci Sports Exercise* (2019) 51:2375–90. doi: 10.1249/MSS.0000000000002116
32. Henriksson A, Johansson B, Radu C, Berntsen S, Igelström H, Nordin K. Is it Safe to Exercise During Oncological Treatment? A Study of Adverse Events During Endurance and Resistance Training–Data From the Phys-can Study. *Acta Oncol* (2021) 60:96–105. doi: 10.1080/0284186X.2020.1851046
33. Schmitz KH, Ahmed RL, Troxel AB, Cheville A, Lewis-Grant L, Smith R, et al. Weight Lifting for Women at Risk for Breast Cancer-Related Lymphedema: A Randomized Trial. *JAMA - J Am Med Assoc* (2010) 304:2699–705. doi: 10.1001/jama.2010.1837
34. Aukland K, Reed RK. Interstitial-Lymphatic Mechanisms in the Control of Extracellular Fluid Volume. *Physiol Rev* (1993) 73:1–78. doi: 10.1152/physrev.1993.73.1.1
35. Schmid-Schonbein GW. Microlymphatics and Lymph Flow. *Physiol Rev* (1990) 70:987–1028. doi: 10.1152/physrev.1990.70.4.987
36. Lane K, Worsley D, McKenzie D. Exercise and the Lymphatic System: Implications for Breast-Cancer Survivors. *Sports Med* (2005) 35:461–71. doi: 10.2165/00007256-200535060-00001
37. Coates G, 'O'Brodovich H, Goeree G. Hindlimb and Lung Lymph Flows During Prolonged Exercise. *J Appl Physiol* (1993) 75:633–8. doi: 10.1152/jappl.1993.75.2.633
38. Gerritsen JKW, Vincent AJPE. Exercise Improves Quality of Life in Patients With Cancer: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Br J Sports Med* (2016) 50:796–803. doi: 10.1136/bjsports-2015-094787
39. Buffart LM, Kalter J, Sweegers MG, Courneya KS, Newton RU, Aaronson NK, et al. Effects and Moderators of Exercise on Quality of Life and Physical Function in Patients With Cancer: An Individual Patient Data Meta-Analysis of 34 Rcts. *Cancer Treat Rev* (2017) 52:91–104. doi: 10.1016/j.ctrv.2016.11.010
40. del-Rosal-Jurado A, Romero-Galisteo R, Trinidad-Fernández M, González-Sánchez M, Cuesta-Vargas A, Ruiz-Muñoz M. Therapeutic Physical Exercise Post-Treatment in Breast Cancer: A Systematic Review of Clinical Practice Guidelines. *J Clin Med* (2020) 9:1239. doi: 10.3390/jcm9041239
41. Nelson NL. Breast Cancer-Related Lymphedema and Resistance Exercise: A Systematic Review. *J Strength Conditioning Res* (2016) 30:2656–65. doi: 10.1519/JSC.0000000000001355
42. Bloomquist K, Adamsen L, Hayes SC, Lillelund C, Andersen C, Christensen KB, et al. Heavy-Load Resistance Exercise During Chemotherapy in Physically Inactive Breast Cancer Survivors at Risk for Lymphedema: A Randomized Trial. *Acta Oncol* (2019) 58:1667–75. doi: 10.1080/0284186X.2019.1643916
43. Bloomquist K, Oturai P, Steele ML, Adamsen L, Møller T, Christensen KB, et al. Heavy-Load Lifting: Acute Response in Breast Cancer Survivors at Risk for Lymphedema. *Med Sci sports Exercise* (2018) 50:187–95. doi: 10.1249/MSS.0000000000001443
44. Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 Explanation and Elaboration: Guidance for Protocols of Clinical Trials. *BMJ (Clinical Res ed)* (2013) 346:e7586. doi: 10.1136/bmj.e7586
45. Moher D, Schulz KF, Altman DG. The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomized Trials. *Ann Internal Med* (2001) 134:657. doi: 10.7326/0003-4819-134-8-200104170-00011
46. Ramírez-Parada K, Courneya KS, Fernández-Verdejo R, Muñiz S, Sánchez C. Physical Activity Levels and Preferences of Patients With Breast Cancer Receiving Chemotherapy in Chile. *Supportive Care Cancer* (2019) 27:2941–7. doi: 10.1007/s00520-018-4595-1
47. Lagally KM, Robertson RJ. Construct Validity of the OMNI Resistance Exercise Scale. *J Strength Conditioning Res* (2006) 20:252–6. doi: 10.1519/R-17224.1
48. Robertson RJ, Goss FL, Rutkowski J, Lenz B, Dixon C, Timmer J, et al. Concurrent Validation of the OMNI Perceived Exertion Scale for Resistance Exercise. *Med Sci Sports Exercise* (2003) 35:333–41. doi: 10.1249/01.MSS.0000048831.15016.2A
49. Kirkham AA, Bland KA, Zucker DS, Bovard J, Shenkier T, McKenzie DC, et al. "Chemotherapy-Periodized" Exercise to Accommodate for Cyclical Variation in Fatigue. *Med Sci sports Exercise* (2020) 52:278–86. doi: 10.1249/MSS.0000000000002151
50. *Huawei Band 4. Copyright © 1998-2022 Huawei Device Co, Ltd All Rights* (2021). Available at: https://consumer.huawei.com/en/wearables/band4/.
51. Ramírez-Parada K, Mella-Abarca W, Nicoletti-Santoni N, Torres-Riveros G, Villagrán-Gutierrez I, Petric-Guajardo M, et al. Implementación De Un Modelo De Atención Kinesiológico, Temprano Y Prospectivo, En Personas Con Cáncer De Mama. *Rev Cirugía* (2019) 71:476–81. doi: 10.35687/s2452-45492019005607
52. Levenhagen K, Davies C, Perdomo M, Ryans K, Gilchrist L. Diagnosis of Upper Quadrant Lymphedema Secondary to Cancer: Clinical Practice Guideline From the Oncology Section of the American Physical Therapy Association. *Phys Ther* (2017) 97:729–45. doi: 10.1093/ptj/pzx050
53. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. *J Natl Cancer Institute* (1993) 85:365–76. doi: 10.1093/jnci/85.5.365
54. Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, et al. The European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality-of-Life Questionnaire Module: First Results From a Three-Country Field Study. *J Clin Oncol* (1996) 14:2756–68. doi: 10.1200/JCO.1996.14.10.2756
55. Elisa Irarrázaval M, Rodríguez PF, Fasce G, Silva FW, Waintrub H, Torres C, et al. Calidad De Vida En Cáncer De Mama: Validación Del Cuestionario

BR23 En Chile. *Rev Med Chile* (2013) 141:723–34. doi: 10.4067/S0034-98872013000600006
56. Svens B, Lee H. Intra- and Inter-Instrument Reliability of Grip-Strength Measurements: Griptrack™ and Jamar® Hand Dynamometers. *Br J Handb Ther* (2005) 10:47–55. doi: 10.1177/175899830501000202
57. Romero-Dapueto C, Mahn J, Cavada G, Daza R, Ulloa V, Antúnez M. Estandarización De La Fuerza De Prensión Manual En Adultos Chilenos Sanos Mayores De 20 Años. *Rev médica Chile* (2019) 147:741–50. doi: 10.4067/s0034-98872019000600741
58. Mancilla Solorza E, Ramos FS, Morales BP. Association Between Handgrip Strength and Functional Performance in Chilean Older People. *Rev Med Chile* (2016) 144:598–603. doi: 10.4067/S0034-98872016000500007
59. Enright PL. The Six-Minute Walk Test Introduction Standards and Indications 6-Minute Walk Test Versus Shuttle Walk Test Safety Variables Measured Conducting the Test Ensuring Quality Factors That Influence 6-Minute Walk Distance Interpreting the Results Improving the. *Respir Care* (2003) 48:783–5.
60. Schmidt K, Vogt L, Thiel C, Jäger E, Banzer W. Validity of the Six-Minute Walk Test in Cancer Patients. *Int J Sports Med* (2013) 34:631–6. doi: 10.1055/s-0032-1323746
61. Cancer Therapy Evaluation Program (CTEP). Common Terminology Criteria for Adverse Events (CTCAE).V.5.0 [5x7]. In: *Cancer Therapy Evaluation Program (Ctep)*, vol. 155. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (2017). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
62. Cohen J. *Statistical Power Analysis for the Behavioral Sciences. 2nd Ed*. New York: Associates New York, USA (1988).
63. Gutknecht M, Herberger K, Klose K, Purwins S, Dietz D, Blome C, et al. Cost-of-Illness of Patients With Lymphoedema. *J Eur Acad Dermatol Venereol* (2017) 31:1930–5. doi: 10.1111/jdv.14442
64. Shih YCT, Xu Y, Cormier JN, Giordano S, Ridner SH, Buchholz T a., et al. Incidence, Treatment Costs, and Complications of Lymphedema After Breast Cancer Among Women of Working Age: A 2-Year Follow-Up Study. *J Clin Oncol* (2009) 27:2007–14. doi: 10.1200/JCO.2008.18.3517
65. Stout NL, Pfalzer LA, Springer B, Levy E, McGarvey CL, Danoff JV. Breast Cancer-Related Lymphedema: Comparing Direct Costs of a Prospective Surveillance Model and a Traditional Model of Care. *Phys Ther* (2012) 92:152–63. doi: 10.2522/ptj.20100167
66. Baumann FT, Reike A, Hallek M, Wiskemann J, Reimer V. Does Exercise Have a Preventive Effect on Secondary Lymphedema in Breast Cancer Patients Following Local Treatment? - A Systematic Review. *Breast Care* (2018) 13:380–5. doi: 10.1159/000487428
67. Azhar SH, Lim HY, Tan BK, Angeli V. The Unresolved Pathophysiology of Lymphedema. *Front Physiol* (2020) 11:137. doi: 10.3389/fphys.2020.00137
68. Mihara M, Hara H, Hayashi Y, Narushima M, Yamamoto T, Todokoro T, et al. Pathological Steps of Cancer-Related Lymphedema: Histological Changes in the Collecting Lymphatic Vessels After Lymphadenectomy. *PLoS One* (2012) 7:e41126. doi: 10.1371/journal.pone.0041126
69. Iyer D, Jannaway M, Yang Y, Scallan JP. Lymphatic Valves and Lymph Flow in Cancer-Related Lymphedema. *Cancers* (2020) 12:1–18. doi: 10.3390/cancers12082297
70. De Sire A, Losco L, Cigna E, Lippi L, Gimigliano F, Gennari A, et al. Three-Dimensional Laser Scanning as a Reliable and Reproducible Diagnostic Tool in Breast Cancer Related Lymphedema Rehabilitation: A Proof-of-Principle Study. *Eur Rev Med Pharmacol Sci* (2020) 24:4476–85. doi: 10.26355/eurrev_202004_21030
71. Invernizzi M, Runza L, De Sire A, Lippi L, Blundo C, Gambini D, et al. Integrating Augmented Reality Tools in Breast Cancer Related Lymphedema Prognostication and Diagnosis. *J Visualized Experiments* (2020) 2020:1–9. doi: 10.3791/60093
72. Cave J, Paschalis A, Huang CY, West M, Copson E, Jack S, et al. A Systematic Review of the Safety and Efficacy of Aerobic Exercise During Cytotoxic Chemotherapy Treatment. *Supportive Care Cancer* (2018) 26:3337–51. doi: 10.1007/s00520-018-4295-x
73. Zdenkowski N, Tesson S, Lombard J, Lovell M, Hayes S, Francis PA, et al. Supportive Care of Women With Breast Cancer: Key Concerns and Practical Solutions. *Med J Aust* (2016) 205:471–5. doi: 10.5694/MJA16.00947
74. Bland KA, Zadravec K, Landry T, Weller S, Meyers L, Campbell KL. Impact of Exercise on Chemotherapy Completion Rate: A Systematic Review of the Evidence and Recommendations for Future Exercise Oncology Research. *Crit Rev Oncol/Hematol* (2019) 136:79–85. doi: 10.1016/j.critrevonc.2019.02.005
75. West H. Telemedicine in Oncology: Delivering on an Overdue Promise in the COVID-19 Era. *Front Oncol* (2020) 10:578888. doi: 10.3389/fonc.2020.578888
76. Mella-Abarca W, Barraza-Sánchez V, Ramírez-Parada K. Telerehabilitation for People With Breast Cancer Through the COVID-19 Pandemic in Chile. *Ecancermedicalscience* (2020) 14:1–8. doi: 10.3332/ECANCER.2020.1085
77. Ng AH, Ngo-Huang A, Vidal M, Reyes-Garcia A, Liu DD, Williams JL, et al. Exercise Barriers and Adherence to Recommendations in Patients With Cancer. *JCO Oncol Pract* (2021) 17:e972–81. doi: 10.1200/OP.20.00625
78. Loughney LA, West MA, Kemp GJ, Grocott MP, Jack S. Exercise Interventions for People Undergoing Multimodal Cancer Treatment That Includes Surgery. *Cochrane Database Syst Rev* (2018) 12:CD012280. doi: 10.1002/14651858.CD012280.pub2

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 14 April 2022
doi: 10.3389/fonc.2022.740787

# Feasibility for Using Thermography Throughout an Exercise Program in Mastectomized Patients

*Maria Jane das Virgens Aquino*[1*], *Paula Michele dos Santos Leite*[1], *Ingrid Kyelli Lima Rodrigues*[1] and *Josimari Melo DeSantana*[2*]

[1] Physiotherapy Department, Federal University of Sergipe, São Cristóvão, Brazil, [2] Physical Therapy Department, Graduate Program in Health Science, Graduate Program in Physiological Science, Federal University of Sergipe, São Cristóvão, Brazil

OPEN ACCESS

**Edited by:**
Julio de la Torre,
Comillas Pontifical University, Spain

**Reviewed by:**
Desislava Kostova-Lefterova,
Aleksandrovska University Hospital, Bulgaria
Sheeja Francis,
Jerusalem College of Engineering, India

***Correspondence:**
Maria Jane das Virgens Aquino
mjvafisio@gmail.com
Josimari Melo DeSantana
desantanajm@gmail.com

**Specialty section:**
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

**Received:** 13 July 2021
**Accepted:** 07 March 2022
**Published:** 14 April 2022

**Citation:**
das Virgens Aquino MJ, dos Santos Leite PM, Lima Rodrigues IK and DeSantana JM (2022) Feasibility for Using Thermography Throughout an Exercise Program in Mastectomized Patients. Front. Oncol. 12:740787. doi: 10.3389/fonc.2022.740787

**Introduction:** Breast cancer is the most common in the female population. Physical training is safe and indicated after surgical treatment for breast cancer. During exercise, body temperature changes due to tissue metabolic activity; in this sense, infrared thermography is used to map the thermal patterns of the body surface.

**Objective:** This study aimed to evaluate the feasibility of using thermography during a physical rehabilitation program in mastectomized patients by analyzing the change in body temperature caused by physical exercise in the breast region.

**Methodology:** This is a simple and covert clinical trial, in which the sample was constituted for convenience. The women were submitted to a supervised physical exercise protocol, three times a week, for 20 sessions. They were evaluated in the first, tenth, and twentieth sessions in relation to changes in body temperature in the breast region (infrared thermography).

**Results:** Twenty patients who underwent mastectomy surgery were recruited. No patient had drain infection, scar dehiscence, or lymphedema, and only one patient had seroma removed. The mean age was 50.45 ± 2.00 years, and the body mass index (BMI) was 28.95 ± 1.11 kg/m$^2$. In the body thermography of the patients' breast region, no significant difference was observed when comparing the thermograms of the plastron region of the patients in the first, tenth, and twentieth sessions ($p = 0.201$). However, when comparing the plastron region with the control breast, a reduction in temperature was observed in the operated region in the first ($p = 0.012$) and tenth sessions ($p = 0.004$).

**Conclusion:** Through this study, we can conclude that the use of infrared thermography is viable for the analysis of the body temperature of mastectomized patients during a supervised physical exercise protocol and, therefore, suggest that this instrument is increasingly used in the cancer public.

**Keywords: breast neoplasm, exercise, feasibility studies, mastectomy, thermography**

## INTRODUCTION

Breast cancer has the most incidences in both the world and Brazilian female population, except for non-melanoma skin cancer. In Brazil, 66,280 new cases of breast cancer are estimated each year of 2020–2021 biennium (1).

Although physical exercise has a positive impact on the physical and psychological wellbeing of breast cancer survivors, physical activity declines significantly after diagnosis and increases slowly after treatment period (2), and then physical exercise plays a critical role in the recovery. A guideline published by the American College of Sports Medicine (3) states that physical training is safe during and after cancer surgical treatment and improves functionality, quality of life, and oncological fatigue (4).

A systematic review and meta-analysis described the effects of physical exercise interventions after adjuvant therapy in women with breast cancer (5). The main results were improvements in fatigue, cardiorespiratory fitness, quality of life, physical and social/emotional function, and self-reported physical activity, which were sustained for 3 months or more after the intervention. Walking, horse riding, yoga, and water-based and resistance exercises were among the interventions carried out in the studies.

During exercise, body temperature changes due to the metabolic activities of human tissues (6). Thermography is a widely used technique to assess temperature in the tissues because it is a non-invasive and non-painful procedure (7). In oncological patients, this technique can be performed as a complementary examination to detect breast cancer; however, mammography is the primary screening modality (8, 9). Among all pseudo colors, the white region represents a higher temperature indicating an anomalous region of the breast (9, 10). Thermography images offer functional information associated with vasodilatation, hyper-perfusion, and hyper-metabolism (6).

Therefore, infrared thermography (IRT) is a comfortable and safe procedure that aims to capture infrared radiation emitted by a surface to measure different patterns of temperature distribution (11, 12). Besides that, this instrument has been highlighted in terms of its use for rehabilitation purposes, evaluation, and re-evaluation after treatment (9, 13, 14).

IRT is not an instrument that shows anatomic abnormalities, but it is a method that demonstrates physiological changes (15) and allows mapping thermal patterns, that is, thermograms, on body surface (16). Thermograms showing increased nipple temperature, hot spots, and vascular changes may indicate serious breast problems (10). A temperature difference of 1°C between thermograms can be used to detect changes in the breast tissue (17).

A systematic review evaluated skin temperature ($T_{sk}$) during physical exercise in healthy individuals through IRT and observed that there is no homogeneous response in $T_{sk}$ between different regions of the body. The duration and intensity of the proposed activity, the function of the body region, and the need for heat loss are responsible for this heterogeneity (18).

A scientific gap is observed in relation to the clinical safety of therapeutic exercise in post-mastectomized women's rehabilitation. For a long time, it was recommended that women would remain on bed rest so that they would not have problems with healing or risk of developing metastases. Therefore, this study aims to assess the feasibility of using thermography during a physical rehabilitation program in mastectomized patients by analyzing the change in body temperature promoted by physical exercise in the breast region (postoperative inflammation). Through the use of IT, we can safely conduct the patient's physical rehabilitation process.

## MATERIAL AND METHOD

This is a single-blinded arm of a randomized clinical trial; the sample was obtained by convenience, composed of patients who were looking for treatment at Associação de Amigos da Oncologia (AMO), a non-profit organization in Aracaju, Sergipe, Brazil. Two investigators participated in the study. Investigator 1 performed the initial, middle, and final assessments, and investigator 2 was responsible for supervising the exercise protocol.

The present study was approved by the Committee of Ethics for Research in Humans of the Federal University of Sergipe (2.537.651). Participants signed an informed consent according to Resolution 466 from National Health Council. CONSORT's recommendations for pilot and feasibility trials were used in the preparation of this study (19).

Women with an anatomopathological diagnosis of breast cancer who underwent either radical or total mastectomy surgery were included. They could have been submitted or not to adjuvant chemotherapy and were admitted at rehabilitation service after drain removal or until 4 months after surgery and with the healed surgical incision. Women with breast reconstruction, metastasis, and bilateral breast cancer or those who presented an orthopedic or rheumatologic problem that represented significant functional alterations (e.g., bursitis, fibromyalgia, and lupus) were excluded.

Women underwent a physical exercise protocol, three times a week, individually, for 50 min, totaling 20 sessions. This quantity of sessions represents the recommended time to achieve improvement in mobility and postoperative pain that may impair the performance of radiotherapy, if indicated, as often used in clinical practice. The format for each exercise session consisted of global stretching, followed by active-free kinesiotherapy, resistance training in the upper and lower limbs, and, finally, a relaxation period with stretching activities (20, 21) (**Figure 1**).

Exercises promoted active shoulder abduction, adduction, flexion, extension, and internal and external rotation movements; elbow flexion and extension; and hip and knee flexion and extension and plantar flexion (20). Three series of 8 to 15 repetitions were done with a resting interval of 1 min, for each exercise. Resistance exercises using 1- and 2-kg dumbbells, 1-kg shin pads, and elastic bands with mild and moderate resistance were inserted as patients presented flexion above

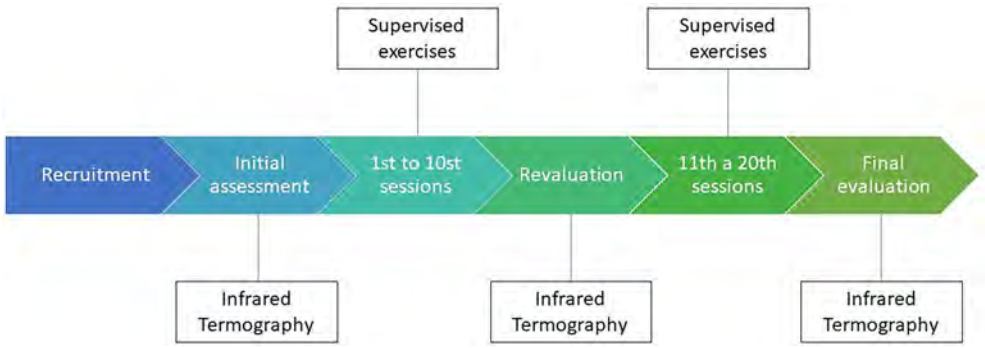



**FIGURE 1** | Study timeline.

90°, abduction above 45°, and external rotation of the shoulder above 30° in the upper limb ipsilateral to the surgery. In the lower limbs, this therapeutic modality started in the first session.

If some discomfort was perceived by the patient during physical exercises, such as nausea, vomiting, excessive sweating, fatigue, or unbearable pain, exercise was interrupted until the patient felt better. Physical exercises were performed, respecting the limit of each patient involved in the study. The physical therapist responsible for the treatment was trained for it and had 4 years of experience in this clinical area. Patients also received all orientations that should be adopted with the operated region and the ipsilateral arm to the surgery. Likewise, they were encouraged to freely perform aerobic activities, such as walking, dancing, or swimming.

IRT evaluates body abnormalities through alterations in superficial blood flow in affected areas (15). This measurement was performed in the 1st (baseline), 10th (middle), and 20th (final) sessions of the patients, and a thermographic camera FLIR Systems T420$^{TM}$ (Wilsonville, OR, USA) was used as assisted by a computer. This equipment allows images with a spatial resolution of 1.4 mrad obtained by visualization of hot spots of 1.4 mm to 1 m of distance, using standard lenses without additional lenses: thermal sensitivity of 0.05°C in 30°C, a spectral range of 7.5–13 µm, and digital video of 320 × 240 pixels.

All images were analyzed and displayed in a palette of 85–100 colors, with a thermal window of 0.15°C for each color. Thermal sensitivity of 0.51°C per color tone was used based on rainbow type (colorful palette) colorimetric scale, in which the cores were from the warmest to the coldest (FLIR QuickReport$^{TM}$ v. 1.2 and FLIR Reporter$^{TM}$ v. 8.5, FLIR Systems, Inc.). Colors indirectly indicate the degree of distribution of local's skin cutaneous perfusion.

The room's temperature was maintained at between 19°C and 21°C (22) and relative humidity of 80%. Women remained in this location, sitting in a chair, with their breasts uncovered for 15 min before images were obtained for acclimatization and to avoid sweating bias. The camera was placed on a tripod at 75 cm in height and 100 cm away from the patient, and the thermograms were captured including both breasts in a single image (11, 14). For the assessment, women were instructed to not apply lotions, makeup, or sunscreen on the skin; not smoke 2 h before evaluation; not drink coffee or alcohol; not perform any physical activity; and inform if they have used any medication. They were also instructed to not palpate, press, and rub the skin at any moment until the thermographic examination was completed (14, 15).

When analyzing the images, a region of interest (IR) was standardized on both breasts of each patient, allowing to calculate the mean and SD of the temperature of that region. IR was defined based on the size of the surgical incision for each patient. The upper limit consisted of the axillary line, and the lower limit was the line drawn at the height of the xiphoid process. The unpaired t-test was used to compare temperatures on the plastron region with the contralateral breast. The repeated-measures ANOVA test was performed to compare temperature alterations during rehabilitation protocol. $p < 0.05$ value was considered statistically significant.

## RESULTS

Twenty patients who submitted to mastectomy for breast cancer removal were recruited. None of these patients presented drain infection, scar dehiscence, or lymphedema, and only one patient needed seroma removal.

Patients' mean age was 50.45 ± 2.00 years, and body mass index (BMI) was 28.95 ± 1.11 (kg/m$^2$). In general, patients started physical therapy only 38.25 ± 23.13 days after the surgical procedure, 60% underwent a simple mastectomy, 70% had their right breast operated on, 70% were married, 100% used the drain, and 85% underwent neoadjuvant chemotherapy (**Table 1**).

In body thermographic examinations of the patients' breast region, no significant difference was observed when comparing thermograms of patients' plastron region at the first, tenth, and twentieth sessions ($p = 0.201$). However, when comparing the plastron region with the control breast, a significant increase in temperature was observed in the operated region at the first ($p = 0.012$) and tenth sessions ($p = 0.004$) (**Table 2**).

**TABLE 1 |** Sociodemographic, clinical, and surgical data of treated patients (n = 20). .

| Variable | Mean ± SD |
|---|---|
| ***Age (years)*** | 50.45 ± 2.00 |
| ***Weight (kg)*** | 70.52 ± 3.16 |
| ***Height (cm)*** | 1.58 ± 0.01 |
| ***Body mass index (kg/m$^2$)*** | 28.95 ± 1.11 |
| ***Time for beginning treatment (days)*** | 38.25 ± 23.13 |
| ***Marital status*** | **n (%)** |
| *Single* | 3 (15) |
| *Married* | 14 (70) |
| *Divorced* | 1 (5) |
| *Widow* | 2 (10) |
| ***Type of surgery*** | **n (%)** |
| *Simple mastectomy* | 12 (60) |
| *Radical mastectomy* | 8 (40) |
| ***Local of surgery*** | **n (%)** |
| *Right* | 14 (70) |
| *Left* | 6 (30) |
| ***Neoadjuvant chemotherapy*** | **n (%)** |
| *Yes* | 17 (85) |
| *No* | 3 (15) |
| ***Neoadjuvant radiotherapy*** | **n (%)** |
| *Yes* | 0 |
| *No* | 20 (100) |
| ***Lymphedema*** | **n (%)** |
| *Yes* | 0 |
| *No* | 20 (100) |

*Values presented as mean ± SD, and absolute and relative values (%).*

In the qualitative analysis of thermograms, we found that all patients (100% of images analyzed) had white and red areas in the region of the surgical scar, which represents higher temperatures at this location, with probable relation to the postoperative inflammatory process (**Figure 2**).

Regarding the feasibility of using thermography in the population studied, no adverse effects were reported by patients; in addition, 100% of participants adhered to the IRT technique and to the proposed physiotherapeutic proposals.

## DISCUSSION

IRT is a non-invasive method that can be performed in any age range, but in the oncologic public, it is mostly used as a complementary exam to cancer clinical diagnosis (7). A study that evaluated the accuracy and reliability of IRT on assessment of breast of women with cancer suggested that it can be used for the purpose of (non-diagnostic) assessment of skin temperature before and after therapeutic procedures or to establish correlations with other clinical variables (17). Biologically, the metabolic rate of cancer cells is higher than that of normal cells. Consequently, tumors act as a heat source, increasing the surface temperatures around the cancerous area, which can be seen as a hot spot in a thermal image (23).

According to the International Academy of Clinical Thermology (IACT), IRT contributes to the evaluation of vascularization in solid organs, diseases in soft tissues, and pain studies (23). In our study, there was an important change in the temperature of the plastron region, which was higher in comparison to that of the control breast. Physical exercise practice, however, caused a reduction in plastron temperature, while the control breast remained unchanged from baseline temperature values. This measurement offers safety and feasibility for a program of supervised rehabilitation after mastectomy. However, body temperature is not the only variable that should be analyzed; the assessment of pain, range of motion, muscle flexibility, and functionality, among others, are also important for the evolution of patients.

After thermographic evaluation of patellar and Achilles tendons of healthy individuals (24), there was an increase in tendon's temperature immediately after running with an

**TABLE 2 |** Cutaneous temperature in degrees in plastron region and control breast at 1st, 10th, and 20th sessions.

| Breast | 1st session | p | 10th session | p | 20th session | p | p (RM) |
|---|---|---|---|---|---|---|---|
| **Control** | 32.91 ± 1.59 | 0.012* | 32.82 ± 1.25 | 0.004* | 32.36 ± 1.44 | 0.067 | 0.201 |
| **Operated** | 34.26 ± 1.12 | | 34.17 ± 1.13 | | 33.47 ± 0.90 | | |

*Data presented in mean ± SD.*
*RM, repeated measures.*
**p ≤ 0.05. Unpaired t-test and ANOVA for repeated-measures test.*

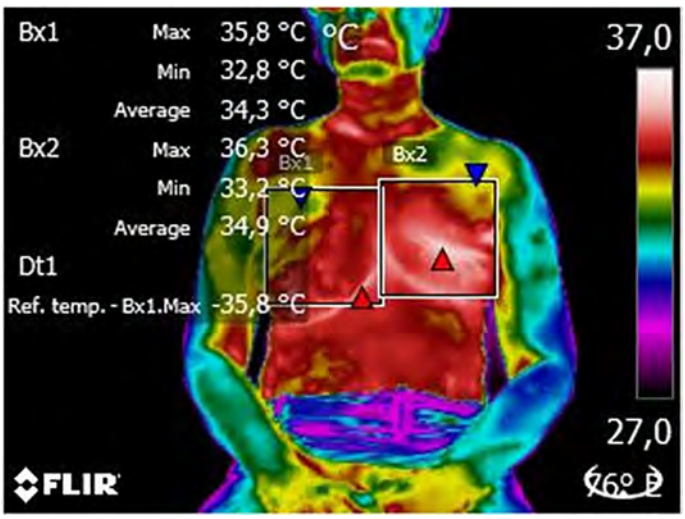



**FIGURE 2** | Thermogram of an evaluated patient thermogram. From this image, it is possible to observe the delimitation of the region of interest (white squares), the color palette (frow lowest to highest temperature) used to identify probable changes and the patient's position (seated) to capture the image. On the right, we can see the patient´s breasts (in red and yellow) while on the left, there is the plastron region (in red) and the mastectomy scar (in white).

eccentric overload when compared to basal values prior to exercise, between a trained group that used eccentric overload and a non-trained group during 3 days of running. In addition, the study found no difference in temperature between the limbs in the individuals who practiced running. In our study, we can observe that the change in temperature between the breast and the plastron region presents a difference greater than 1°C in the three evaluated moments. This does not mean that the carcinogenesis process is still taking place, as we have to consider the presence of inflammatory mediators in the recent postoperative period. It is noteworthy that the temperature of the plastron region reduces along with each evaluation, which corroborates the hypothesis mentioned above about the influence of the inflammatory cascade.

Fernandes and collaborators (12) monitored changes in the skin temperature of healthy individuals during exercise in 28 body regions of interest (forehead, face, chest, abdomen, back, neck, lumbar spine, hands, forearms, arms, thighs, and legs) and observed a reduction in temperature in most regions of interest after 10 min of activity, with the exception of the lower limbs. However, after an hour of recovery, in the anterior view of the hands and thighs and the posterior view of the legs, there was a significant increase in temperature in relation to the pre-exercise. Nevertheless, in mastectomized women, we noticed that the temperature reduction in the plastron region was maintained after physical exercise protocol, which consisted of 20 supervised training sessions. Furthermore, there was no significant change in body temperature that represents a risk or contraindication to exercise because it promotes the process of carcinogenesis or increases local inflammation.

The application of IRT requires some important care to avoid biases during the acquisition of thermograms. One of them is the regulation of body temperature. Our patients remained for a certain time in acclimatization in a temperature-controlled room and received guidance on the care they should adopt before performing IRT. Thus, sweating would not become a confounding factor at the time of data interpretation. Studies show that the evaporation of sweat that occurs during exercise corresponds to a physiological mechanism to reduce skin temperature ($T_{sk}$) (18, 25). In a thermoneutral environment and at rest, $T_{sk}$ tends to remain in balance, and the change in it may be indicative of the presence of some pathological state (26).

The limitations of our study include the difficulty in segmenting the breast area, since each person has different anatomy, given the amorphous nature of breast structure (10) and the small sample size (n = 20). However, it is important to highlight the innovative character of our study, since there is no article that has assessed the change in body temperature during and after a supervised program of exercises for mastectomized women. Another gap in the literature concerns the lack of studies that address physical therapy treatments and the use of IRT, especially aimed at the breast region. Through this measure, we can show the feasibility of using IRT throughout an exercise program in mastectomized patients by bringing safety to perform physical rehabilitation from a clinical and physiological point of view.

## CONCLUSION

We can conclude that the use of IRT is feasible for the analysis of the body temperature of mastectomized patients during and after a supervised physical exercise protocol. Thus, we reinforce the possibility for considering this instrument to be increasingly used for evaluating oncology patients.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Committee of Ethics for Research in Humans of the Federal University of Sergipe (2.537.651). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

MA: first authorship. PL: equal contribution. IR: equal contribution. JDS: senior authorship. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

## REFERENCES


1. Instituto Nacional do Câncer (Brasil. *Estimativa 2020 - Incidência De Câncer No Brasil*. Rio de Janeiro: INCA (2019).
2. Penttinen H, Utriainen M, Kellokumpu-Lehtinen P, Raitanen J, Sievanen H, Niander R, et al. Effectiveness of a 12-Month Exercise Intervention on Physical Activity and Quality of Life of Breast Cancer Survivors; Five-Year Results of the BREX-Study. *In Vivo* (2019) 33:881–8. doi: 10.21873/invivo.11554
3. Schimitz KH, Courneya KS, Mattews C, Demark-Wahnefried W, Galvão DA, Pinto BM, et al. American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors. *Med Sci Sports Exerc* (2010) 42(7):1409–26. doi: 10.1249/MSS.0b013e3181e0c112
4. Schmitz KH, Ahmed RL, Troxel AB, Cheville A, Lewis-Grant L, Smith R, et al. Weight Lifting for Women at Risk for Breast Cancer-Related Lymphedema: A Randomized Trial. *JAMA - J Am Med Assoc* (2010) 304:2699–705. doi: 10.1001/jama.2010.1837
5. Lahart IM, Metsios GS, Nevill AM. Physical Activity for Women With Breast Cancer After Adjuvant Therapy (Review). *Cochrane Database Syst Rev* (2018) 103:1–913. doi: 10.1002/14651858.CD011292.pub2
6. Han F, Shi G, Liang C, Wang L, Li K. A Simple and Efficient Method for Breast Cancer Diagnosis Based on Infrared Thermal Imaging. *Cell Biochem Biophys* (2014) 71:491–8. doi: 10.1007/s12013-014-0229-5
7. Garduño-Ramón MA, Vega-Mancilla SG, Morales-Henández LA, Osornio-Rios RA. Supportive Noninvasive Tool for the Diagnosis of Breast Cancer Using a Thermographic Camera as Sensor. *Sensors* (2017) 17:1–21. doi: 10.3390/s17030497
8. Alikhassi A, Hamidpour SF, Firouzmand M, Navid M, Eghbal M. Prospective Comparative Study Assessing Role of Ultrasound Versus Thermography in Breast Cancer Detection. *Breast Dis* (2018) 37:191–6. doi: 10.3233/BD-180321
9. Dua G, Mulaveesala R. Applicability of Active Infrared Thermography for Screening of Human Breast: A Numerical Study. *J Biomed Opt* (2018) 23:1–10. doi: 10.1117/1.JBO.23.3.037001
10. Gogoi UR, Bhowmik MK, Bhattacharjee D, Ghosh AK. Singular Value Based Characterization and Analysis of Thermal Patches for Early Breast Abnormality Detection. *Australas Phys Eng Sci Med* (2018) 41:861–79. doi: 10.1007/s13246-018-0681-4
11. Dos Santos Heberle AB, Ichisato SMT, Nohama P. Avaliação Da Mama Na Lactação Por Termografia E Presença De Dor. *Acta Paul Enferm* (2015) 28:256–63. doi: 10.1590/1982-0194201500043
12. Fernandes AA, Amorim PRS, Brito CJ, Sillero-Quintana M, Marins JCB. Regional Skin Temperature Response to Moderate Aerobic Exercise Measured by Infrared Thermography. *Asian J Sports Med* (2016) 7:1–8. doi: 10.5812/asjsm.29243
13. Weigert M, Nitzsche N, Kunert F, Lösch C, Schulz H. The Influence of Body Composition on Exercise-Associated Skin Temperature Changes After Resistance Training. *J Therm Biol* (2018) 75:112–9. doi: 10.1016/j.jtherbio.2018.05.009
14. Ra JY, Sun A, Lee GH, Kim TU, Lee SJ, Hyun JK. Skin Temperature Changes in Patients With Unilateral Lumbosacral Radiculopathy. *Ann Rehabil Med* (2013) 37:355–63. doi: 10.5535/arm.2013.37.3.355
15. Nahm FS. Infrared Thermography in Pain Medicine. *Korean J Pain* (2013) 26:219–22. doi: 10.3344/kjp.2013.26.3.219
16. Figueiredo AAA, Nascimento JG, Malheiros FC, Ignacio LHS, Fernandes HC, Guimarães G. Breast Tumor Localization Using Skin Surface Temperatures From a 2D Anatomic Model Without Knowledge of the Thermophysical Properties. *Comput Methods Programs BioMed* (2019) 172:65–77. doi: 10.1016/j.cmpb.2019.02.004
17. Guirro RRG, Vaz MMOLL, Neves LMS, Dibai-Filho AV, Carrara HHA, Guirro ECO. Accuracy and Reliability of Infrared Thermography in Assessment of the Breasts of Women Affected by Cancer. *J Med Syst* (2017) 41:1–6. doi: 10.1007/s10916-017-0730-7
18. Fernandes AA, Amorim PRS, Prímola-Gomes TN, Sillero-Quintana M, Fernández CI, Silva R, et al. Evaluation of Skin Temperature During Exercise by Infrared Thermography: A Systematic Review. *Rev Andal Med Deport* (2012) 5:113–7. doi: 10.1016/S1888-7546(12)70017-5
19. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. Declaração CONSORT 2010: Extensão Para Ensaios Piloto Randomizados E De Viabilidade. *BMJ* (2016) 355:i5239. doi: 10.1136/bmj.i5239
20. Battaglini C, Bottaro M, Dennehy C, Barfoot D, Shields E, Kirk D, et al. Efeitos do Treinamento De Resistência Na Força Muscular E Níveis De Fadiga Em Pacientes Com Câncer De Mama. *Rev Bras Med Esporte* (2006) 12:153–8. doi: 10.1590/S1517-86922006000300009
21. Giganti MG, Tresoldi I, Sorge R, Melchiorri G, Triossi T, Masuelli L, et al. Physical Exercise Modulates the Level of Serum MMP-2 and MMP-9 in Patients With Breast Cancer. *Oncol Lett* (2016) 12:2119–26. doi: 10.3892/ol.2016.4887
22. Haddad DS, Brioschi ML, Arita ES. Thermographic and Clinical Correlation of Myofascial Trigger Points in the Masticatory Muscles. *Dentomaxillofac Radiol* (2012) 41:621–9. doi: 10.1259/dmfr/98504520
23. Umadevi V, Raghavan SV, Jaipurkar S. Framework for Estimating Tumor Parameters Using Thermal Imaging. *Indian J Med Res* (2011) 134:725–31. doi: 10.4103/0971-5916.91012
24. Sanz-López F, Martínez-Amat A, Hita-Contreras F, Valero-Campo C. Thermographic Assessment of Eccentric Overload Training Within Three Days of a Running Session. *J Strength Cond Res* (2016) 30:504–11. doi: 10.1519/JSC.0000000000001071
25. Silva AG, Albuquerque MR, Brito CJ, Oliveira SAF, Stroppa GM, Sillero-Quintana M, et al. Resposta Térmica Da Pele Ao Exercício Em Remo Ergômetro De Alta Versus Moderada Intensidade Em Homens Fisicamente Ativos. *RPCD* (2017) 17:125–37. doi: 10.5628/rpcd.17.S4A.125
26. Marins JCB, Moreira DG, Cano SP, Quintana MS, Soares DD, Fernandes AA, et al. Time Required to Stabilize Thermographic Images at Rest. *Infrared Phys Technol* (2014) 65:30–5. doi: 10.1016/j.infrared.2014.02.008


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 02 May 2022
doi: 10.3389/fonc.2022.753729

# Establishing Minimal Clinically Important Differences for the Quality of Life Instrument in Patients With Breast Cancer QLICP-BR (V2.0) Based on Anchor-Based and Distribution-Based Methods

*Fei Li*[1†], *Yuxi Liu*[1†], *Chonghua Wan*[1*], *Jiali Zhou*[1], *Jianfeng Tan*[1] *and Huanwei Chen*[2]

[1] Research Center for Quality of Life and Applied Psychology, Key Laboratory for Quality of Life and Psychological Assessment and Intervention, School of Humanities and Management, Guangdong Medical University, Dongguan, China, [2] Central Hospital of Guangdong Nongken, The six wards of Medical Oncology, Zhanjiang, China

OPEN ACCESS

**Edited by:**
Julio de la Torre,
Comillas Pontifical University, Spain

**Reviewed by:**
Tsuguo Iwatani,
National Cancer Centre, Japan
Agnieszka Guzik,
University of Rzeszow, Poland

***Correspondence:**
Chonghua Wan
wanchh@hotmail.com

[†]These authors have contributed equally to this work and share first authorship

**Specialty section:**
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

**Received:** 05 August 2021
**Accepted:** 04 April 2022
**Published:** 02 May 2022

**Citation:**
Li F, Liu Y, Wan C, Zhou J, Tan J and Chen H (2022) Establishing Minimal Clinically Important Differences for the Quality of Life Instrument in Patients With Breast Cancer QLICP-BR (V2.0) Based on Anchor-Based and Distribution-Based Methods. Front. Oncol. 12:753729. doi: 10.3389/fonc.2022.753729

**Objective:** To determine the minimal clinically important differences (MCIDs) for the breast cancer scale QLICP-BR (V2.0) among the Quality of Life Instruments system for cancer patients (QLICP), which consist of the general module of 32 items classifying into 4 domains and the specific module of 10 items.

**Methods:** According to the scoring rule of QLICP-BR (V2.0), the scores of each domain and the overall scale were calculated. The MCIDs of this scale were established by anchor-based and distribution-based methods. The anchor method used the Q29 item in the EORTC QLQ-C30 scale as anchors and defined the treatment effectiveness of the anchor-based method using criteria A (one level improvement after treatment) and B (at least one level improvement after treatment), while methods of effect size (ES), standard error of measurement (SEM), and reliability change index (RCI) were used in distribution-based methods.

**Results:** Using the anchor-based method, according to standard A, the MCIDs of the physical domain (PHD), psychological domain (PSD), social domain (SOD), common symptoms and side effect domain (SSD), core/general module (CGD), specific domain (SPD), and the total score (TOT) were 16.24, 11.37, 11.31, 12.07, 11.49, 10.69, and 11.23 respectively; according to standard B, the MCIDs of PHD, PSD, SOD, SSD, CGD, SPD, and TOT were 18.88, 15.14, 14.10, 14.50, 13.93, 12.17, and 14.23 respectively. In the distribution-based MCID study, when ES = 0.8, the MCID values of each domain and the total score of the scale were 9.14, 10.34, 8.34, 10.54, 6.79, 9.73, and 6.96 respectively. The MCIDs calculated when a SEM of 1.96 was used as the intermediary index were 8.38, 11.04, 8.67, 10.00, 7.44, 9.83, and 7.81. The MCIDs calculated when a RCI of 1.96 was used as the intermediary index were 11.84, 15.61, 12.27, 14.14, 10.52,

13.90, and 11.05. Additionally, the MCID value calculated by the two standards of the anchor method was similar to 0.8 ES, 1.96 SEM, and 1.96 RCI.

**Conclusion:** Using the anchor-based method, 0.8ES, 1.96SEM, and 1.96RCI have a better effect on the minimal clinically important difference of breast cancer scale and were recommended to be the preferred methods for establishing MCID.

**Keywords: breast cancer, quality of life, minimal clinically important difference, anchor-based method, distribution-based method**

## INTRODUCTION

Breast cancer is one of the most common malignant tumors in women and a leading cause of cancer-related deaths. The age of breast cancer diagnosis is between 40 and 60 years old. Each year more than 1.7 million women are diagnosed and more than 500 000 die from breast cancer, making it the leading cause of cancer death among women globally (1, 2). There are more than 1.67 million new cases of breast cancer in women worldwide in 2012, ranking first place in the incidence of female malignant tumors (3–5). In 2018, breast cancer accounted for 11.6% of all cancer deaths worldwide (6). In China, the incidence of breast cancer has increased in recent years with the development of society and economy, changes in lifestyle, and ecological environment. From 2003 to 2008, the standardized incidence of breast cancer in Chinese women increased from 21.17/100,000 to 26.26/100,000, an increase of 17.65%. The incidence of breast cancer declined slightly in 2009, but from 2010 to 2012, it rose sharply to 30.43/100,000, an increase of 43.74% compared with 2003. The average annual rate of change in breast cancer mortality over the past 10 years was 3.87 percent (7). It can be seen from this that the incidence and mortality of breast cancer in China as a whole show a trend of a gradual increase, and the burden of disease is also increasing.

Along with the increasing number of breast cancer patients and the longer survival due to early detection programs and advancement in medical technology, accurately assessing the health-related quality of life (HRQOL) of breast cancer patients is crucial (8–10). By far, the more popular HRQOL tools for breast cancer are the European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30) and the breast cancer-specific module QLQ-BR23, and the American Breast Cancer Quality of Life Measurement Scale FACT-B (10–12).

However, these scales are not fully applicable to the assessment of the quality of life of Chinese people. Therefore, Wan's QOL team developed the Chinese instrument for the breast cancer quality of life measurement QLICP-BR (including the first (13) and second editions), which is one scale of the system of Quality of Life Instruments for cancer patients (QLICP). The second version QLICP-BR (V2.0) is composed of a general module QLICP-GM (V2.0) and a breast cancer-specific module. Among them, QLICP-GM (V2.0) includes 32 items from 10 facets grouped into four domains: physical function (8 items), psychological function (9 items), social function (8 items), and common symptoms and side effects (7 items) (14). The breast cancer-specific module consists of 3 facets and 10 items. The whole scale consists of 5 domains, 13 facets, and 42 items (15). The QLICP-BR (V2.0) has been verified in Mainland China and has good reliability, validity, and responsiveness after testing. It can be used for the determination of the quality of life in patients with breast cancer during the period of onset, treatment, and rehabilitation (15).

In order to reasonably explain the clinical significance of questionnaire measurements and scale scores, as early as 1987, Guyatt et al. proposed to use the Minimal Clinically Important Difference (MCID) as an appropriate benchmark for evaluating important changes in the responsiveness of the scale. The researchers did not define MCID and acknowledged the difficulty of quantifying MCID, indicating that the changes caused by interventions with known efficacy can provide a preliminary estimate. Two years later, Jaeschke, Singer, and Guyatt defined MCID as "the smallest change in the score of the questionnaire dimension recognized by the patient without considering side effects and costs (16)." Thus, clinicians need a systematic approach to assess the perceived benefit of a treatment based on the individual patient's improvement in cost and risk of complications. Ideally, MCID will provide a specific threshold as a treatment target and has been widely used in this regard.

The QLICP-BR (V2.0) has been widely used in China, but MCID has not been developed, so it is not convenient for further applications. The purpose of this study is to use the QLICP-BR (V2.0) scale to develop the minimal clinically important difference (MCID) for breast cancer.

## MATERIALS AND METHODS

### Subjects and Data Collection

This study was based on inpatients with a clinical breast cancer who were diagnosed by pathological examination in the Affiliated Hospital of Guangdong Medical University and the Central Hospital of Guangdong Nongken. The investigator appeared as a doctor and briefly explained the content and

**Abbreviations:** MCID, minimal clinically important differences; QLICP-BR, Quality of Life Instruments system in breast cancer patients; EORTC, European Organization for Research and Treatment; ES, effect size; SEM, standard error of measurement; RCI, reliability change index; PHD, physical domain; PSD, psychological domain; SOD, social domain; SSD, common symptoms and side effect domain; CGD, core/general module; SPD, specific domain; TOT, total; HRQOL, health-related quality of life; ROC curve, receiver operating characteristic.

purpose of the investigation. After obtaining the consent of the patient and signing the informed consent form, the investigator sent the QLICP-BR (V2.0) to the patients to fill in by themselves. In total, 246 patients were included in the study. The inclusion and exclusion criteria are as follows:

Inclusion criteria: (1) Patients with a clear diagnosis, that is, those diagnosed with breast cancer by pathological examination; (2) Good reading and presentation skills, able to fill out questionnaires by themselves; (3) Volunteer to participate in the survey, no mental illness or disturbance of consciousness.

Exclusion criteria: (1) Cognitive and consciousness dysfunction; (2) Those who refuse to participate in the research or those with a low degree of cooperation; (3) At the end of life, combined with other primary cancers, other serious diseases, mental illnesses, etc.; (4) Malignant tumors that frequently metastasize.

In terms of sample size, we use the sample size calculation *formula:*

$$n = \frac{Z_\alpha^2 \times pq}{d^2}$$

p is the effective rate of treatment, q=1-p, d represents the allowable error, and $Z_\alpha$ is the statistical quantity of the significance test. When d = 0.1p and $\alpha$ =0.05, n = $400 \times \frac{q}{p}$. According to experience, p =0.67,q=0.33, So n is equal to 197. In addition, according to the empirical method, the sample size should be 5-10 times that of the variable. The number of items in this scale is 42, and the sample size is suitable for 210-420 cases. The sample size of this investigation is 246 cases, which can meet the statistical requirements of sample size.

## MCIDs of the Anchor-Based Method

The anchor-based method is used to clarify the meaning of the scale's score change by examining the relationship between the scale and the score of another independent measurement tool or other indicators. Anchor-based approaches assess the extent to which changes in measurement instruments correspond to a minimally important change defined by external indicators (17). Anchors are divided into cross-sectional anchors and longitudinal anchors (18). This article is used to compare the efficacy before and after treatment, so the longitudinal anchor was selected. First, the RS (raw score) was scored based on the number of questions contained in each domain and the patient's options. Then, linear transformation was performed using the range method to convert the raw score into a standardized score (SS) with a value between 0 and 100. The formula for calculating the score in each domain is as follows (19):

$$SS = (RS - Min) \times 100/R \; R = Max - Min$$

The Q29 item " How would you rate your overall health during the past week?" in the EORTC QLQ-C30 scale (20) was taken as the anchor and used to calculate the correlation coefficient between Q29 and the QLICP-BR (V2.0) total scale score. Then, patients who differed by one grade (criterion A) and at least one grade (criterion B) in Q29 before and after treatment were screened out. The score difference in each domain before and after treatment was calculated, and the mean of the absolute value of the difference was recorded as MCID. The calculation formula is shown in **Table 1**.

## MCIDs of the Distribution-Based Method

The distribution-based method uses the evaluation tool sample data distribution (variation) to determine the MCID from a statistical point of view. Commonly used indicators for calculating variation include effect size (ES), standard error of measurement (SEM), and reliability change index (RCI). The calculation formula and corresponding MCID calculation are as follows:

$$ES = \frac{\bar{x}_1 - \bar{x}_0}{\sqrt{\sum (x_0 - \bar{x}_0)^2 / n - 1}} \; MCID = ES \times SD_{baseline}$$

$X_0$ is the baseline score of the respondent;

$\bar{x}_0$ is the mean baseline score of the respondent; $SD_{baseline}$ is the standard deviation of the baseline score of the respondent; $\bar{x}_1$ is the mean score of the respondent after treatment; and n is the sample size (21–23). In the health-related quality of life assessments, the ES is currently a relatively recognized parameter in determining the importance of group or individual changes. There is also an accepted standard for ES judgment: 0.2 is a small effect; 0.5 is a medium effect; 0.8 or greater is a large effect (23).

$$SEM = \sqrt{1 - r} \times \sqrt{\sum (x_0 - \bar{x}_0)^2 / n - 1} \; MCID = X \times SD_{\text{baseline}} \times \sqrt{1 - r}$$

Where r is the reliability coefficient of the evaluation questionnaire and the test-retest reliability coefficient is generally used. If the test-retest reliability coefficient is unknown, the Cronbach coefficient can be used instead. X can be 1 (small effect), 1.96 (medium effect), or 2.77 (large effect) (22–24).

**TABLE 1** | Calculation formula of MCID based on anchor method.

| Standard | Sample size *n* | Anchor difference *D* (Q29 Score difference) | Scale field score difference *d* | Mean ($\overline{|d|}$) |
|---|---|---|---|---|
| A: One level away | $n_1$ | $D_1$=$X_1$- $X_0$=±1 | $x_1$-$x_0$ | $\frac{d_1 + d_2 + \ldots + d_{n_1}}{n_1}$ |
| B: At least one level away | $n_2$ | $D_2$=$X_1$-$X_0$=±1,2,3,4,5,6 | $x_1$-$x_0$ | $\frac{d_1 + d_2 + \ldots + d_{n_2}}{n_2}$ |

$$RCI = \frac{\bar{x}_1 - \bar{x}_0}{\sqrt{2(SEM)^2}} \quad MCID = X \times SD_{baseline} \times \sqrt{2(1 - r)}$$

RCI, which is the change in questionnaire score divided by the square root of the standard measurement error (25, 26).

## Statistical Software

This survey used Epidata3.1 software to input data and SPSS 25.0 software to organize and analyze the data. The scores of various domains and the total score of the scale and the MCID value of breast cancer were calculated.

# RESULTS

## Social-Demographic and Clinical Characteristics of Breast Cancer Patients

A total of 246 breast cancer patients were investigated in this study, all of which were women. The age distribution was between 17-77 years old. The average age was 50.07 ± 10.25. Among the patients, 5.3% were under 30 years old, 10.2% were between 30 and 40 years old, 37.0% were between 40 and 50 years old, 29.3% were between 50 and 60 years old, and 18.3% were over 60 years old. The household economy was mostly medium, accounting for 67.9% of the total population. The occupations were mostly workers and farmers, with 20 workers (8.1%) and 112 farmers (45.5.0%), respectively. The majority of patients were married, accounting for 97.2%. The most common ethnicity was Han, accounting for 97%. The distribution of educational level was mostly in Middle school or High school, accounting for 60.2%. Medical insurance was mostly used in medical forms, accounting for 91.9%. Medical treatment insurance included medical insurance for urban residents, medical insurance for urban workers, cooperative medical treatment, and commercial medical insurance. TNM stages were distributed between I-IV stages, with 53 being stage I (21.5%), 86 stage II (35.0%), 54 stage III (22.0%), and 27 stage IV (11.0%), respectively. See **Table 2** in detail.

## MCIDs of the Anchor-Based Method

The correlation coefficient between the Q29 and QLICP-BR (V2.0) score in the EORTC QLQ-C30 scale was calculated using the Q29 item "How do you evaluate your total health condition in the past week" as an anchor, and r = 0.651 was obtained.

According to standard A, patients with a difference of one grade on Q29 before and after treatment were screened, 116 cases were effective, and the QLICP-BR (V2.0) scores in each domain and the total scale score difference before and after treatment were calculated.

In regard to socio-demographic and clinical characteristics of the sample based on Standard A, 116 (100%) patients were female, 78 (67.2%) were aged between 40 and 60 years old. Most of them had medium family income (69%) and had middle school education (64.7%). 54 (46.6%) were farmers, 100 (94.8%) were married, 112 (96.6%) were Han nationality, 107 (92.2%) had medical insurance. On clinical stages, the cases distributed in the four stages of TNM I, II, III, IV were 29, 38, 21, 14, respectively.

According to standard B, patients with at least one grade difference in Q29 before and after treatment were screened. A total of 166 patients were effective. The scores of QLICP-BR (V2.0) in each domain and the total scale score difference before and after treatment were calculated.

In terms of socio-demographic and clinical characteristics of the sample based on Standard B, all of the 166 patients were female, and 112 (67.5%) were aged between 40 and 60 years old. Most of them had medium family income (67.5%) and middle school education (64.4%). 81(48.8%) were farmers, 160 (96.4%) were married, 162 (97.6%) were Han nationality, and 155(93.4%) had medical insurance. On clinical stages, the cases distributed in the four stages of TNM I, II, III, IV were 38, 59, 31, 22, respectively.

**TABLE 2** | Socio-demographic and clinical characteristics of the Sample (n = 246).

| Characteristics | N | % | Characteristics | N | % |
|---|---|---|---|---|---|
| **Gender** | | | **Marital status** | | |
| Male | 0 | 0 | Married | 239 | 97.2 |
| Female | 246 | 100 | Others | 7 | 2.8 |
| **Age** | | | **Ethnicity** | | |
| ≤30 | 13 | 5.3 | Han | 237 | 96.3 |
| 30-40 | 25 | 10.2 | Others | 9 | 3.7 |
| 40-50 | 91 | 37.0 | **Education** | | |
| 50-60 | 72 | 29.3 | Primary school | 65 | 26.4 |
| ≥60 | 45 | 18.3 | Middle school or High school | 148 | 60.2 |
| | | | College/University | 33 | 13.4 |
| **Economic** | | | **Medical insurance** | | |
| Poor | 52 | 21.1 | Self-paid/Private insurance | 20 | 8.1 |
| Fair | 167 | 67.9 | Medical insurance | 226 | 91.9 |
| High | 27 | 11.0 | **TNM** | | |
| **Occupation** | | | I | 53 | 21.5 |
| Worker | 20 | 8.1 | II | 86 | 35.0 |
| Farmer | 112 | 45.5 | III | 54 | 22.0 |
| Others | 114 | 46.3 | IV | 27 | 11.0 |

Then, the mean and standard deviation of the difference between the scores of each domain and the total scale under the two standards were calculated and the mean of the difference as MCID was recorded. The results are shown in **Table 3**. According to standard A, the MCID values of physical domain (PHD), psychological domain (PSD), social domain (SOD), common symptoms and side effect domain (SSD), core/general module (CGD), specific domain (SPD) and the total scale (TOT) were 16.24, 11.37, 11.31, 12.07, 11.49, 10.69 and 11.23, respectively. According to standard B, the MCID values of PHD, PSD, SOD, SSD, CGD, SPD and TOT were 18.88, 15.14, 14.10, 14.50, 13.93, 12.17, and 14.23, respectively.

## MCIDs of the Distribution-Based Methods

The distribution-based method estimates MCID based on the observed distribution of score changes. The MCID results of breast cancer were calculated using three variation indexes: ES, SEM, and RCI. We calculated the MCID results using the three indicators respectively as shown in **Tables 4**–**6**.

As can be seen from **Table 4**, when ES = 0.2, the MCID values for each domain and the total scale were 2.28, 2.58, 2.09, 2.63, 1.70, 2.43 and 1.74, respectively. When ES = 0.5, the MCID values of each domain and the total scale were 5.71, 6.46, 5.22, 6.56, 4.25, 6.08 and 4.35, respectively. When ES = 0.8, the MCID values of each domain and the total scale were 9.14, 10.34, 8.34, 10.54, 6.79, 9.73 and 6.96, respectively.

The MCIDs calculated for above domains/the total when SEM was used as an intermediary index were 4.27, 5.63, 4.43, 5.10, 3.80, 5.01 and 3.99, respectively. The MCIDs calculated for above domains/the total when 1.96SEM was used as the intermediary index were 8.38, 11.04, 8.67, 10.00, 7.44, 9.83 and 7.81, respectively.

The MCIDs calculated for above domains/the total when RCI was used as the intermediary index were 6.04, 7.96, 6.26, 7.21, 5.37, 7.09 and 5.64, respectively. The MCIDs calculated for above domains/the total when 1.96RCI was used as the intermediary index were 11.84, 15.61, 12.27, 14.14, 10.52, 13.90 and 11.05, respectively. The MCIDs calculated for above domains/the total when 2.77RCI was used as the intermediary index were 16.74, 22.06, 17.33, 19.98, 14.87, 19.64, and 15.62, respectively.

# DISCUSSIONS

MCID is a difference score that is sufficient to reflect the effect on patients after clinical treatment, and its main function is to help clinical and research personnel to determine whether changes in the score of the scale have clinical significance. Clearly, clinicians

**TABLE 3 |** The MCID value of QLICP-BR (V2.0) determined by anchor-based method ($n_A$ = 116, $n_B$ = 166).

| Domain | Items | Standard A $\bar{x} \pm s$ | Standard B $\bar{x} \pm s$ | Standard A MCID | Standard B MCID |
|---|---|---|---|---|---|
| Physical domain (PHD) | 8 | 16.24 ± 10.65 | 18.88 ± 12.31 | 16.24 | 18.88 |
| Psychological domain (PSD) | 9 | 11.37 ± 9.24 | 15.14 ± 12.51 | 11.37 | 15.14 |
| Social domain (SOD) | 8 | 11.31 ± 8.08 | 14.10 ± 13.80 | 11.31 | 14.10 |
| Common symptoms and side effect domain (SSD) | 7 | 12.07 ± 8.69 | 14.50 ± 12.08 | 12.07 | 14.50 |
| Core/general module (CGD) | 32 | 11.49 ± 7.41 | 13.93 ± 9.26 | 11.49 | 13.93 |
| Specific domain (SPD) | 10 | 10.69 ± 8.34 | 12.17 ± 9.83 | 10.69 | 12.17 |
| Total (TOT) | 42 | 11.23 ± 7.47 | 14.23 ± 9.63 | 11.23 | 14.23 |

**TABLE 4 |** The MCID value of QLICP-BR (V2.0) determined by ES (n = 246).

| Domain | $SD_{baseline}$ | 0.2ES | 0.5ES | 0.8ES |
|---|---|---|---|---|
| Physical domain (PHD) | 11.42 | 2.28 | 5.71 | 9.14 |
| Psychological domain (PSD) | 12.92 | 2.58 | 6.46 | 10.34 |
| Social domain (SOD) | 10.43 | 2.09 | 5.22 | 8.34 |
| Common symptoms and side effect domain (SSD) | 13.17 | 2.63 | 6.56 | 10.54 |
| Core/general module (CGD) | 8.49 | 1.70 | 4.25 | 6.79 |
| Specific domain (SPD) | 12.16 | 2.43 | 6.08 | 9.73 |
| Total (TOT) | 8.70 | 1.74 | 4.35 | 6.96 |

**TABLE 5 |** The MCID value of QLICP-BR (V2.0) determined by SEM (n = 246).

| Domain | r | $SD_{baseline}$ | SEM | 1.96SEM |
|---|---|---|---|---|
| Physical domain (PHD) | 0.86 | 11.42 | 4.27 | 8.38 |
| Psychological domain (PSD) | 0.81 | 12.92 | 5.63 | 11.04 |
| Social domain (SOD) | 0.82 | 10.43 | 4.43 | 8.67 |
| Common symptoms and side effect domain (SSD) | 0.85 | 13.17 | 5.10 | 10.00 |
| Core/general module (CGD) | 0.80 | 8.49 | 3.80 | 7.44 |
| Specific domain (SPD) | 0.83 | 12.16 | 5.01 | 9.83 |
| Total (TOT) | 0.79 | 8.70 | 3.99 | 7.81 |

**TABLE 6 |** The MCID value of QLICP-BR (V2.0) determined by RCI (n = 246).

| Domain | r | $SD_{baseline}$ | RCI | 1.96RCI | 2.77RCI |
|---|---|---|---|---|---|
| Physical domain (PHD) | 0.86 | 11.42 | 6.04 | 11.84 | 16.74 |
| Psychological domain (PSD) | 0.81 | 12.92 | 7.96 | 15.61 | 22.06 |
| Social domain (SOD) | 0.82 | 10.43 | 6.26 | 12.27 | 17.33 |
| Common symptoms and side effect domain (SSD) | 0.85 | 13.17 | 7.21 | 14.14 | 19.98 |
| Core/general module (CGD) | 0.80 | 8.49 | 5.37 | 10.52 | 14.87 |
| Specific domain (SPD) | 0.83 | 12.16 | 7.09 | 13.90 | 19.64 |
| Total (TOT) | 0.79 | 8.70 | 5.64 | 11.05 | 15.62 |

also need a systematic way to assess the perceived benefit of a certain treatment based on individual patient improvement relative to both cost and risk of complications (27). At the same time, it can also further explain the score of the scale, so as to provide a scientific basis for clinical and scientific researchers to deal with patients of different degrees more specifically (28). Therefore, it is critical that the MCID score is a valid and stable measure. A low MCID may result in overestimating the positive effects of treatment, whereas a high MCID value may incorrectly classify patients as failing to respond to treatment when in fact the treatment was beneficial (26).

In clinical studies, a lot of methodological approaches have been reported to calculate MCID such as the anchor-based method, distribution-based method, expert opinion method, literature analysis method, etc (29). In general, methodological approaches can be classified into two broad groups: anchor-based and distribution-based (29–32). The two kinds of methods can get a variety of results from different angles, which is conducive to comparison and user selection according to the situation. But each method has its advantages and disadvantages. An anchor-based approach relies on external calibration, which must be easy to interpret and strong in relation to the quality of life. But choosing different anchors will result in different MCID values. The distribution-based method takes into account the measurement error and also has a specific calculation formula, which is easy to implement, but easily affected by sample size (33, 34). Therefore, most scholars recommend applying multiple methods where the anchoring method is used as the main method and the distribution method is used as a supplement to determine MCID.

The EORTC-QLQ-C30 is a 30-item health-related quality of life questionnaire for cancer patients. Q30(How would you rate your overall quality of life during the past week)? and Q29 (How would you rate your overall health during the past week)? in the scale are comprehensive items and are often used as anchors. We calculated the correlation coefficients of Q29, Q30 and QLICP-BR (V2.0) scales respectively. The correlation coefficients were 0.651 and 0.588, respectively. Obviously, the correlation coefficient between Q29 and scale score is larger. At the same time, the content of Q29 is easier to be understood by patients. Therefore, we choose Q29 as the anchor. In this study, using the anchor-based method, according to standard A, the MCIDs of PHD, PSD, SOD, SSD, CGD, SPD and TOT were 16.24, 11.37, 11.31, 12.07, 11.49, 10.69 and 11.23, respectively; ranging from 10.69 to 16.24 points. According to standard B, the MCIDs of PHD, PSD, SOD, SSD, CGD, SPD and TOT were 18.88, 15.14, 14.10, 14.50, 13.93, 12.17 and 14.23, respectively, ranging from 12.17 to 18.88 points. It can be seen that according to criterion A, patients are more likely to obtain meaningful clinical change values; in other words, the quality of life of breast cancer patients is more likely to be judged as improved.

However, the selected anchor Q29 and the total scale score correlation coefficient r was 0.651, which is not too high and may affect the reliability of MCID. In addition, the selected anchor is relatively single, which may cause unstable results. So, we continued to use the distribution-based method and calculated the MCID under the three variation indicators of ES, SEM, and RCI.

In the distribution-based MCID study, When ES = 0.2, ES = 0.5, and ES = 0.8 were used as intermediary indicators, the MCID values of the scores for each domain and the overall scale were ranged from 1.70 to 2.63 points, 4.25 to 6.56 points, and 6.79 to 10.54 points, respectively. The MCIDs of the scores for each domain and the overall scale calculated with SEM and 1.96SEM as the intermediary indicators were ranged from 3.80 to 5.63 points and 7.44 to 11.04 points, respectively. When RCI, 1.96RCI, and 2.77RCI were used as the intermediary index, the calculated MCIDs of the scores for each domain and the overall scale were ranged from 5.37 to 7.96 points, 10.52 to 15.61 points, and 14.87 to 22.06 points, respectively.

In the evaluation of clinical efficacy, the clinicians and researchers can judge clinical significance by these MCIDs. Taking 0.5ES method as an example, the overall QOL of patients can be evaluated as clinical significance when the QOL change before and after treatment is over 4.35 points for its MCID is 4.35. Similarly, the MCID of the MFSI-SF identified by Chan A et al. ranged from 4.50 to 10.79 points, and can be used to interpret the clinical significance of fatigue deterioration in patients with breast cancer (35). Quinten C et al. evaluated the short and long-term effects of chemotherapy on the reported quality of life (QOL) and patient-clinician symptom reporting in older breast cancer patients with an MCID of 10. Results showed that symptom burden and diminished QOL in an older breast cancer population receiving adjuvant TC chemotherapy are short-lived and disappear after a while with no long-term differences compared to a similar population not receiving chemotherapy (36).

In this study, anchor method and distribution method were used to calculate MCID of breast cancer. When the MCID calculated by anchor method is smaller than that calculated by distribution method or the correlation coefficient between the selected anchor and the measured scale is small (the absolute value r at least 0.5 is currently recommended), the results of the distribution method are recommended as the MCIDs of breast

cancer (37). In the calculation of MCID, the anchor method is generally preferred. However, the distribution method is also considered comprehensively if there is no good anchor or the number of patients is not large.

In summary, the MCID value calculated by the two standards of the anchor method was similar to 0.8ES, 1.96SEM, and 1.96RCI. Therefore, these indicators should be given priority in the development of MCID for breast cancer.

Similar results have also been obtained in developing MCID for breast cancer in foreign countries. Alexandre Chan et al. used the anchor-based method, distribution-based method, and ROC curve method to develop the MCID of breast cancer, and the results showed that the MCID of the MFSI-SF identified by all ranged from 4.50 to 10.79 points (38). Yin Ting Cheung et al. used the anchor-based method, distribution-based method, and ROC curve method to develop MCID for breast cancer, and the results were as follows: the estimates of 6.9-10.6 points as MCID can facilitate the interpretation of patient-reported cognitive weakness and sample size in future studies (39). These results are similar to the result of our study, but the MCID value of breast cancer we developed was relatively higher than that of the foreign results. This may be caused by the use of different scales whose scores ranging from 0 to 100 and cultural differences between China and foreign countries.

From the results obtained, we conclude that the MCID value calculated by the two standards of the anchor-based method was similar to 0.8ES, 1.96SEM, and 1.96RCI of the distribution-based methods. Therefore, when selecting the minimal clinical important difference for breast cancer patients, the results of the anchor-based method can be used preferentially, also 0.8ES, 1.96SEM, 1.96RCI of distribution-based methods can be used.

Of course, this study has certain limitations. The methods used in this study include the anchor-based method and the distribution-based method. Other methods can also be used to formulate MCID such as the ROC curve method and the response cumulative distribution function method. Additionally, the sample size of this subject research can be expanded to make the MCID more stable. In future studies, the sample size of breast cancer patients will be expanded, and multiple methods will be used to jointly develop MCID for breast cancer, so as to ensure more stable results.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The study protocol and the informed consent form were approved by the IRB (Institutional Review Board) of the affiliated hospital of Guangdong Medical University (PJ2012052, YJYS2019010). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

CW designed the study. FL, JZ, and HC performed the data collection. FL,JT, and YL performed data analyses and drafted the manuscript. CW revised the manuscript deeply. All authors contributed to interpreting the data, and have read and approved the final manuscript.

## FUNDING

This study is supported by the National Natural Science Foundation of China (71974040, 81273185), Dongguan Science and Technology of Social Development Program (20211800905102).

## ACKNOWLEDGMENTS

In carrying out this research project, we have received substantial assistance from Prof. Gary Lyman from Hutchinson Institute for Cancer Outcomes Research, and Prof. David Cella, Benjamin J. Arnold and Hiramatsu Toshiko at the Center on Outcomes, Research, and Education (CORE), and many staffs at the Central Hospital of Guangdong Nongken. We sincerely acknowledge all the support.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.753729/full#supplementary-material

## REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global Cancer Statistics, 2012. *CA Can J Clin* (2015) 65:87–108. doi: 10.3322/caac.21262
2. El-Hashimi D, Gorey KM. Yoga-Specific Enhancement of Quality of Life Among Women With Breast Cancer: Systematic Review and Exploratory Meta-Analysis of Randomized Controlled Trials. *J Evid Base Integr Med* (2019) 24:1–9. doi: 10.1177/2515690X19828325
3. Shi J, Liang D, Li DJ. Epidemiological Status of Global Female Breast Cancer. *China Cancer* (2017) 26(09):683–90. doi: 10.11735/j.issn.1004-0242.2017.09.A006
4. Qing C, Shunping L, Min W, Liu L, Gang C, Abdelaziz M, et al. Health-Related Quality of Life Among Women Breast Cancer Patients in Eastern China. *BioMed Res Int* (2018) 2018:1452635. doi: 10.1155/2018/1452635
5. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer Incidence and Mortality Worldwide: Sources, Methods and Major Patterns in GLOBOCAN 2012. *Int J Cancer* (2015) 136:E359–86. doi: 10.1002/ijc.29210

6. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2018) 68 (6):394–424. doi: 10.3322/caac.21492
7. He MY. *Analysis of Epidemic Trend With Breast Cancer and Research on the Effect of Postoperative Radiotherapy*. Hengyang, Hunan Province: University of South China (2019).
8. Yusuf A, Ahmad Z, Keng SL. Quality of Life in Malay and Chinese Women Newly Diagnosed With Breast Cancer in Kelantan, Malaysia. *Asian Pac J Cancer Prev* (2013) 14(1):435–40. doi: 10.7314/APJCP.2013.14.1.435
9. Perry S, Kowalski TL, Chang CH. Quality of Life Assessment in Women With Breast Cancer: Benefits, Acceptability and Utilization. *Health Qual Life Outcome* (2017) 5:24. doi: 10.1186/1477-7525-5-24
10. Chen Q, Li S, Wang M, Liu L, Chen G. Health-Related Quality of Life Among Women Breast Cancer Patients in Eastern China. *BioMed Res Int* (2018) 2018:1452635. doi: 10.1155/2018/1452635
11. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A Quality-of-Life Instrument for Use in International Clinical Trials in Oncology. *J Natl Cancer Inst* (1993) 85(5):365–76. doi: 10.1093/jnci/85.5.365
12. Wan C, Zhang D, Yang Z, Tu X, Tang W, Feng C, et al. Validation of the Simplified Chinese Version of the FACT-B for Measuring Quality of Life for Patients With Breast Cancer. *Breast Cancer Res Treat* (2007) 106(3):413–8. doi: 10.1007/s10549-007-9511-1
13. Wan C, Yang Z, Tang X, Zou T, Chen D, Zhang D, et al. Development and Validation of the System of Quality of Life Instruments for Cancer Patients: Breast Cancer (QLICP-Br). *Sup Care Cancer* (2009) 17(4):359–66. doi: 10.1007/s00520-008-0478-1
14. Wu J, Hu L, Zhang G, Liang Q, Meng Q, Wan C. Development and Validation of the Nasopharyngeal Cancer Scale Among the System of Quality of Life Instruments for Cancer Patients (QLICP-NA V2.0): Combined Classical Test Theory and Generalizability Theory. *Qual Life Res* (2016) 25(8):2087–100. doi: 10.1007/s11136-016-1251-4
15. Wan C. Research Status on the Second Version of the System of Quality of Life Instruments for Cancer Patients QLICP (V2.0). *J Guangdong Med Univ* (2020) 38(05):511–7. doi: 10.3969/j.issn.1005-4057.2020.05.001
16. King MT. A Point of Minimal Important Difference (MID): A Critique of Terminology and Methods. *Expert Rev Pharmacoecon Outcome Res* (2011) 11 (2):171–84. doi: 10.1586/erp.11.9
17. Huang IC, Liu JH, Wu AW, Wu MY, Leite W, Hwang CC. Evaluating the Reliability, Validity and Minimally Important Difference of the Taiwanese Version of the Diabetes Quality of Life (DQOL) Measurement. *Health Qual Life Outcome* (2008) 6(1):87. doi: 10.1186/1477-7525-6-87
18. Crosby RD, Kolotkin RL, Williams GR. Defining Clinically Meaningful Change in Health-Related Quality of Life. *J Clin Epidemiol* (2003) 56 (5):395–407. doi: 10.1016/S0895-4356(03)00044-1
19. Wan CH, Yu YL, Tan JF, Meng Q, Huang XP. *Introductions on Quality of Life Research-Measurements·Assessments·Improvements*. Beijing: Science Press (2016).
20. Zawisza K, Tobiasz-Adamczyk B, Nowak W, Kulig J, Jedrys J. Validity and Reliability of the Quality of Life Questionnaire (EORTC QLQ C30) and its Breast Cancer Module (EORTC QLQ Br23). *Ginekol Pol* (2010) 81(4):262–7.
21. Jaeschke R, Singer J, Guyatt GH. Measurement of Health Status. Ascertaining the Minimal Clinically Important Difference. *Control Clin Trial* (1989) 10 (4):407–15. doi: 10.1016/0197-2456(89)90005-6
22. Sprangers MA, Moinpour CM, Moynihan TJ, Patrick DL, Revicki DA. Clinical Significance Consensus Meeting Group. Assessing Meaningful Change in Quality of Life Over Time: A Users' Guide for Clinicians. *Mayo Clin Proc* (2002) 77(6):561–71. doi: 10.4065/77.6.561
23. Xue HH, Yang Z, Wan CH, Xu QA, Xu CZ, Chen Y. The Method of Making Minimum Difference of Clinical Importance (MCID) Based on Scale Score. *Chin J Health Stat* (2019) 36(3):436–40. doi: CNKI: SUN: ZGWT.0.2019-03-035
24. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the Significance of Changes in Health-Related Quality-of-Life Scores. *J Clin Oncol* (1998) 16 (1):139–44. doi: 10.1200/JCO.1998.16.1.139
25. Guyatt GH, Osaba D, Wu AW, Wyrwich KW, Norman GR. Methods to Explain the Clinical Significance of Health Status Measures. *Mayo Clin Proc* (2002) 77(4):371–83. doi: 10.4065/77.4.371
26. Jacobson NS, Truax P. Clinical Significance: A Statistical Approach to Defining Meaningful Change in Psychotherapy Research. *J Consult Clin Psychol* (1991) 59(1):12–9. doi: 10.1037/0022-006X.59.1.12
27. Copay AG, Subach BR, Glassman SD, Polly DWJr, Schuler TC. Understanding the Minimum Clinically Important Difference: A Review of Concepts and Methods. *Spine J* (2007) 7(5):541–6. doi: 10.1016/j.spinee.2007.01.008
28. Yost KJ, Cella D, Chawla A, Holmgren E, Eton DT, Ayanian JZ, et al. Minimally Important Differences Were Estimated for the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) Instrument Using a Combination of Distribution- and Anchor-Based Approaches. *J Clin Epidemiol* (2005) 58(12):1241–51. doi: 10.1016/j.jclinepi.2005.07.008
29. Wright A, Hannon J, Hegedus EJ, Kavchak AE. Clinimetrics Corner: A Closer Look at the Minimal Clinically Important Difference (MCID). *J Man Manipulat Ther* (2012) 20(3):160–6. doi: 10.1179/2042618612Y.0000000001
30. Rai SK, Yazdany J, Fortin PR, Aviña-Zubieta JA. Approaches for Estimating Minimal Clinically Important Differences in Systemic Lupus Erythematosus. *Arthritis Res Ther* (2015) 17(1):143. doi: 10.1186/s13075-015-0658-6
31. Rodrigues JN, Mabvuure NT, Nikkhah D, Shariff Z, Davis TR. Minimal Important Changes and Differences in Elective Hand Surgery. *J Handb Surg Eur Vol* (2015) 40(9):900–12. doi: 10.1177/1753193414553908
32. Engel L, Beaton DE, Touma Z. Minimal Clinically Important Difference: A Review of Outcome Measure Score Interpretation. *Rheum Dis Clin North Am* (2018) 44(2):177–88. doi: 10.1016/j.rdc.2018.01.011
33. Hu GQ, Huang QF, Huang ZN, Sun ZQ. Methods to Determine Minimal Clinically Important Difference. *J Cent South Univ (Medical Science)* (2009) 34 (11):1058–62. doi: 10.3321/j.issn:1672-7347.2009.11.002
34. Wright A, Hannon J, Hegedus EJ, Kavchak AE. Clinimetrics Corner: A Closer Look at the Minimal Clinically Important Difference (MCID). *J Man Manipulat Ther* (2012) 20(3):160–6. doi: 10.1179/2042618612Y.0000000001
35. Chan A, Yo TE, Wang XJ, Ng T, Chae JW, Yeo HL, et al. Minimal Clinically Important Difference of the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) for Fatigue Worsening in Asian Breast Cancer Patients. *J Pain Symptom Manage* (2018) 55(3):992–7.e2. doi: 10.1016/j.jpainsymman.2017.10.014
36. Quinten C, Kenis C, Hamaker M, Coolbrandt A, Brouwers B, Dal Lago L, et al. The Effect of Adjuvant Chemotherapy on Symptom Burden and Quality of Life Over Time; A Preliminary Prospective Observational Study Using Individual Data of Patients Aged ≥70 With Early Stage Invasive Breast Cancer. *J Geriatr Oncol* (2018) 9(2):152–62. doi: 10.1016/j.jgo.2017.10.001
37. Wyrwich KW, Norquist JM, Lenderking WR, Acaster S. Methods for Interpreting Change Over Time in Patient-Reported Outcome Measures. *Qual Life Res* (2013) 22(3):475–83. doi: 10.1007/s11136-012-0175-x
38. Chan A, Yo TE, Wang XJ, Ng T, Chae JW, Yeo HL, et al. Minimal Clinically Important Difference of the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) for Fatigue Worsening in Asian Breast Cancer Patients. *J Pain Symptom Manage* (2018) 55(3):992–7. doi: 10.1016/j.jpainsymman.2017.10.014
39. Cheung YT, Foo YL, Shwe M, Tan YP, Fan G, Yong WS, et al. Minimal Clinically Important Difference (MCID) for the Functional Assessment of Cancer Therapy: Cognitive Function (FACT-Cog) in Breast Cancer Patients. *J Clin Epidemiol* (2014) 67(7):811–20. doi: 10.1016/j.jclinepi.2013.12.011


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 23 May 2022
doi: 10.3389/fonc.2022.815498

# Long-Term Patient Satisfaction and Quality of Life Following Breast Reconstruction Using the BREAST-Q: A Prospective Cohort Study

*Makoto Shiraishi*[1,2], *Yoshihiro Sowa*[1,3*], *Itaru Tsuge*[3], *Takuya Kodama*[4], *Naoki Inafuku*[1] and *Naoki Morimoto*[3]

[1] Department of Plastic and Reconstructive Surgery, University Hospital Kyoto Prefectural University of Medicine, Kyoto, Japan, [2] Department of Plastic and Reconstructive Surgery, Graduate School of Medicine, Mie University, Mie, Japan, [3] Department of Plastic and Reconstructive Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [4] Department of Plastic and Reconstructive Surgery, Fukuchiyama City Hospital, Fukuchiyama, Japan

**Background:** Breast reconstruction is a promising surgical technique to improve health-related quality of life (HRQoL) in patients with breast cancer. However, the long-term risk factors associated with HRQoL after breast surgery are still unclear. Our aim was to evaluate breast satisfaction and HRQoL following breast reconstruction to identify clinical factors associated with each domain of BREAST-Q in the long-term.

**Methods:** Patient-reported BREAST-Q outcomes were analyzed 1 and 5 years after breast reconstruction in a single-blinded, prospective study. Multiple regression analysis was performed to identify the risk and protective factors associated with BREAST-Q scores. These scores at 1 and 5 years were also compared across three types of operation: mastectomy only, tissue expander/implant (TE/Imp), and a deep inferior epigastric perforator (DIEP) flap.

**Results:** Surveys were completed by 141 subjects after 1 year and 131 subjects after 5 years. Compared to mastectomy only, breast reconstruction was significantly associated with greater "Satisfaction with breasts" (TE/Imp, $p < 0.001$; DIEP, $p < 0.001$) and "Psychosocial well-being" (TE/Imp, $p < 0.001$; DIEP, $p < 0.001$), higher body mass index (BMI) resulted in lower "Satisfaction with breasts" ($p = 0.004$), and a history of psychiatric or neurological medication was significantly associated with "Physical well-being" at 1-year postoperatively ($p = 0.02$). At 5 years, reconstructive procedures were significantly positively associated with greater "Satisfaction with breasts" (TE/Imp, $p < 0.001$; DIEP, $p < 0.001$) and "Psychosocial well-being" (TE/Imp, $p = 0.03$; DIEP, $p < 0.001$), and a bilateral procedure was a significant risk factor for lower "Psychosocial well-being" ($p = 0.02$).

**Conclusions:** The results of this study show that breast reconstruction improves "Satisfaction with Breasts" and "Psychosocial well-being" compared to mastectomy. Among all three types of operation, DIEP gave the best scores at 5 years postoperatively. Thus, autologous reconstruction is recommended for promotion of long-term HRQoL after breast surgery.

**Keywords: breast reconstruction, tissue expander, breast implant, DIEP, BREAST-Q, health-related quality of life**

OPEN ACCESS

***Edited by:***
*Mangesh A. Thorat, Guy's and St Thomas' NHS Foundation Trust, United Kingdom*

***Reviewed by:***
*Julio de la Torre, Comillas Pontifical University, Spain*
*Marco Invernizzi, University of Eastern Piedmont, Italy*
*Alessandro de Sire, University of Magna Graecia, Italy*

***Correspondence:**
*Yoshihiro Sowa*
*sowawan@koto.kpu-m.ac.jp*

***Specialty section:***
*This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology*

***Received:*** *15 November 2021*
***Accepted:*** *20 April 2022*
***Published:*** *23 May 2022*

***Citation:***
*Shiraishi M, Sowa Y, Tsuge I, Kodama T and Inafuku N, Morimoto N (2022) Long-Term Patient Satisfaction and Quality of Life Following Breast Reconstruction Using the BREAST-Q: A Prospective Cohort Study. Front. Oncol. 12:815498. doi: 10.3389/fonc.2022.815498*

# INTRODUCTION

More than 2 million women worldwide receive a new diagnosis of breast cancer every year (1–3). The number of women surviving breast cancer has increased due to improvements of treatment in many countries, including in Japan (4, 5). Postoperative complications such as lymphoedema, axillary web syndrome (AWS), and fatigue may reduce health-related quality of life (HRQoL) (6–8), but patients also have the opportunity to receive breast reconstruction after mastectomy, which can significantly improve HRQoL (9). Factors associated with HRQoL include satisfaction with appearance, psychological well-being, and physical function. In patients with breast cancer, some studies have shown that aesthetic outcome also influences HRQoL (10, 11).

Multiple questionnaires have been used to measure patient-reported outcomes (PROs) after breast surgery for patients with breast cancer. However, until the turn of the century, few instruments had sufficient evidence for specific use in these patients due to limitations in certain areas, including aesthetics and body perception (12). In 2009, the BREAST-Q questionnaire was developed to meet this need, as a validated PRO measurement specific to breast surgery. Since its release, the BREAST-Q has greatly improved studies of satisfaction with breast surgery from the patient's perspective (13–16).

Previous studies using the BREAST-Q questionnaire have established that breast reconstruction provides higher levels of patient satisfaction. Most of these studies had short follow-up periods of up to 1 year and limited comparison groups (17–25). In addition, satisfaction with breast reconstruction may change, even over a short period of time (26–28). Long-term satisfaction is important after breast reconstruction, but how satisfaction and HRQoL change years after the initial operation is still unclear.

To investigate these issues further, we performed a long-term prospective survey of patients with breast cancer who underwent breast surgery including breast reconstruction. The objective was to evaluate HRQoL in a Japanese population following breast reconstruction to identify clinical factors that predict higher or lower BREAST-Q scores in long-term survivors.

# MATERIAL AND METHODS

## Subjects and Experimental Design

We prospectively analyzed clinical data for all consecutive patients with breast cancer who underwent breast reconstruction performed by three surgeons at a single center from January 2016 to April 2017. Patients were enrolled in the study if they fulfilled the following criteria: (1) age ≥18 years, (2) undergoing mastectomy only or first-time unilateral or bilateral post-mastectomy breast reconstruction using a tissue expander/implant (TE/Imp) or a deep inferior epigastric perforator (DIEP) flap, and (3) not meeting exclusion criteria of surgical complications such as implant loss or flap loss that could affect long-term results, death, or a poor understanding of the study due to severe neurological or psychiatric disorders. For power analysis, a 10-point difference in HRQoL (BREAST-Q) score was taken to indicate a clinically relevant difference (minimally important difference: MID) based on a previous study (29). Using alpha of 0.05, a standard deviation of 5-10 points from our previous study (30) and beta of 0.80, at least 34 patients per arm were required for significance. Advice on statistical analysis was provided by Statista (Kyoto, Japan), a medical statistics support company. As the scheduled date of closure was reached, enrollment was stopped in April 2017 before reaching the planned sample size.

## Data Collection and Measurements

All subjects provided demographic data. Smoking was divided into past and current. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Clinical characteristics, type of breast surgery, therapy after mastectomy (radiotherapy, chemotherapy, and/or hormone therapy), and history of psychiatric or neurological illness and medication were obtained from medical records.

## BREAST-Q Survey

The BREAST-Q is a validated PRO measure developed at Memorial Sloan Kettering Cancer Center and the University of British Columbia (13, 14). We focused on three BREAST-Q domains: "Satisfaction with breasts", "Psychosocial well-being", and "Physical well-being". Each domain score was obtained by transforming the scale item responses with the Q-score software program. The transformed scores range from 0 to 100 and higher scores indicated greater satisfaction or QOL. The Japanese version of the BREAST-Q survey was administered prior to surgery after consultation with the surgical oncologist and plastic surgeon, and at 1 and 5 years after completion of surgery (31). At these time points, surveys were given to patients at an office visit or mailed to the patient's home.

## Statistical Analysis

Statistical analyses were performed using JMP Pro v.14.0 (SAS Institute Inc., Cary, NC) and SPSS v.26.0 (IBM Corp., Armonk, NY). Continuous variables are shown as the mean ± standard deviation (SD) and categorical variables as a number (percentage). A multiple linear regression model was constructed for identification of significant factors for HRQoL. A Mann-Whitney U test was used to compare data between years, and a *post-hoc* Tukey test was used for comparison between operative procedures. $P < 0.05$ was considered to be significant in all analyses.

## Ethics Approval

All procedures were approved by the local research ethics committee (Kyoto Prefectural University of Medicine: IRBMED Number ERB-C-563-1) and were conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects.

# RESULTS

Among 213 potential subjects, 8 were excluded due to implant loss (n=1), flap loss (n=2), and difficulty understanding the study because of severe neurological or psychiatric disorders (n=5). All patients received immediate reconstruction. Questionnaire

surveys were sent to the home addresses of 205 subjects in the year after the operation. Written informed consent and answers were obtained from 141 at 1 year and 131 at 5 years postoperatively, giving response rates of 68.8% and 63.9%, respectively (**Figure 1**).

The demographic and clinical characteristics of the 141 subjects at 1 year and 131 subjects at 5 years are shown in **Table 1**. The subjects were 53.0 ± 12.9 years old and had a BMI of 22.3 ± 3.41 kg/m$^2$. The surgical procedures were TE/implant reconstruction (27.4%), mastectomy only (35.0%), and DIEP flap reconstruction (37.6%). Most patients underwent unilateral surgery (94.9%).

Regression analyses for patient-reported aesthetic satisfaction across 3 domains ("Satisfaction with breasts", "Psychosocial well-being", and "Physical well-being") with mastectomy only, TE/Imp and DIEP at 1- and 5-year follow-up after surgery are listed in **Table 2**. These data were controlled for age, BMI, laterality, type of operation, radiation, chemotherapy, smoking, and psychotic/neurological medical history or medication.

At 1-year postoperatively, "Satisfaction with breasts" was significantly impaired in patients with higher BMI (coefficient (β) -0.20, 95% confidence interval (CI) -1.89 to -0.38, p = 0.004). Compared to mastectomy only, TE/Imp and DIEP were both positively associated with "Satisfaction with breasts" (TE/Imp: β -0.61, 95%CI 16.62 to 30.51, p < 0.001; DIEP: β 0.64, 95% CI 21.31 to 35.81, p < 0.001) and "Psychosocial well-being" (TE/Imp: β 0.43, 95% CI 8.71 to 26.80, p < 0.001; DIEP: β 0.35, 95% CI 7.05 to 25.61, p < 0.001) at 1 year. History or medication for a psychotic/neurological condition was associated with greater "Physical well-being" (β 0.20, 95% CI 2.00 to 22.91, p = 0.02) at 1 year. At 5 years, compared to mastectomy only, TE/Imp and DIEP were positively associated with "Satisfaction with breasts" (TE/Imp: β 0.46, 95% CI 7.62 to 21.62, p < 0.001; DIEP: β 0.64, 95% CI 15.82 to 29.52, p < 0.001) and "Psychosocial well-being" (TE/Imp: β 0.25, 95%CI 0.95 to 20.29, p = 0.03; DIEP: β 0.40,

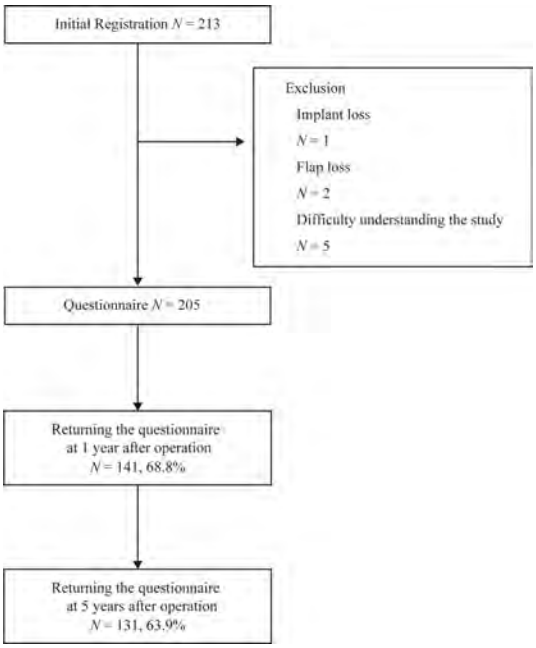



**FIGURE 1** | Inclusion and exclusion of subjects.

**TABLE 1** | Demographics of the subjects.

| Item | Responders after 1 year | | Responders after 5 years | |
|---|---|---|---|---|
| | N | Percent | N | Percent |
| Number of patients | 141 | 100% | 131 | 100% |
| Age (years), mean (SD) | 53.2 (13.1) | | 52.8 (12.8) | |
| BMI (kg/m$^2$), mean (SD) | 22.0 (3.41) | | 22.2 (3.45) | |
| Lesion | | | | |
| Bilateral | 8 | 5.7% | 7 | 5.3% |
| Unilateral | 133 | 94.3% | 124 | 94.7% |
| Type of operation | | | | |
| Mastectomy only | 51 | 36.2% | 45 | 34.4% |
| TE/Imp | 56 | 39.7% | 53 | 40.5% |
| DIEP | 34 | 24.1% | 33 | 25.2% |
| Radiotherapy | | | | |
| No | 108 | 76.6% | 99 | 75.6% |
| Yes | 33 | 23.4% | 32 | 24.4% |
| Chemotherapy/hormone therapy | | | | |
| No | 78 | 55.3% | 68 | 51.9% |
| Yes | 63 | 44.7% | 63 | 48.1% |
| Smoking | | | | |
| Never | 108 | 76.6% | 100 | 76.3% |
| Past | 30 | 21.3% | 29 | 22.1% |
| Current | 3 | 2.1% | 2 | 1.5% |
| Psychotic/neurological medical history or medication | | | | |
| No | 133 | 94.3% | 123 | 93.9% |
| Yes | 8 | 5.7% | 8 | 6.1% |

*SD, Standard deviation; BMI, Body mass index; TE/Imp, tissue expander/implant; DIEP, deep inferior epigastric perforator.*

**TABLE 2 |** Multiple regression analysis of factors associated with increased satisfaction or QOL for BREAST-Q domains.

| Independent Variable | Satisfaction with breasts | | | | Psychological well-being | | | | Physical well-being | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Year 1 | | Year 5 | | Year 1 | | Year 5 | | Year 1 | | Year 5 | |
| | Coefficient | P value | Coefficient | P value | Coefficient | P value | Coefficient | P value | Coefficient | P value | Coefficient | P value |
| Age | 0.03 | 0.73 | 0.12 | 0.23 | 0.06 | 0.55 | -0.07 | 0.51 | -0.12 | 0.24 | -0.78 | 0.49 |
| BMI | -0.20 | 0.004** | -0.07 | 0.40 | -0.07 | 0.39 | -0.02 | 0.85 | 0.01 | 0.91 | 0.17 | 0.08 |
| Lesion | | | | | | | | | | | | |
| Unilateral | Reference | | Reference | | Reference | | Reference | | Reference | | Reference | |
| Bilateral | -0.06 | 0.35 | -0.10 | 0.25 | -0.12 | 0.15 | -0.11 | 0.15 | 0.00 | 0.99 | -0.07 | 0.53 |
| Type of Operation | | | | | | | | | | | | |
| Mastectomy Only | Reference | | Reference | | Reference | | Reference | | Reference | | Reference | |
| TE/ Imp | 0.61 | < 0.001*** | 0.46 | < 0.001*** | 0.43 | < 0.001*** | 0.25 | 0.03* | 0.02 | 0.88 | -0.08 | 0.53 |
| DIEP | 0.64 | < 0.001*** | 0.64 | < 0.001*** | 0.35 | < 0.001*** | 0.40 | < 0.001*** | 0.17 | 0.11 | -0.09 | 0.43 |
| Preoperative Radiation | | | | | | | | | | | | |
| No | Reference | | Reference | | Reference | | Reference | | Reference | | Reference | |
| Yes | 0.02 | 0.79 | 0.10 | 0.26 | 0.01 | 0.87 | 0.12 | 0.17 | 0.08 | 0.37 | 0.16 | 0.10 |
| Chemotherapy | | | | | | | | | | | | |
| No | Reference | | Reference | | Reference | | Reference | | Reference | | Reference | |
| Yes | 0.05 | 0.50 | 0.12 | 0.14 | 0.17 | 0.06 | -0.05 | 0.60 | -0.05 | 0.60 | 0.07 | 0.44 |
| Smoking | | | | | | | | | | | | |
| Never | Reference | | Reference | | Reference | | Reference | | Reference | | Reference | |
| Past | 0.94 | 0.17 | -0.08 | 0.29 | 0.10 | 0.23 | 0.11 | 0.18 | -0.07 | 0.46 | -0.04 | 0.63 |
| Current | -0.54 | 0.43 | 0.03 | 0.71 | 0.06 | 0.47 | 0.05 | 0.57 | -0.07 | 0.54 | -0.01 | 0.93 |
| Psychotic/Neurological Medical History or Medication | | | | | | | | | | | | |
| No | Reference | | Reference | | Reference | | Reference | | Reference | | Reference | |
| Yes | -0.02 | 0.83 | 0.03 | 0.73 | -0.05 | 0.56 | -0.15 | 0.84 | 0.20 | 0.02* | 0.17 | 0.08 |

*BMI, Body mass index; TE/Imp, tissue expander/implant; DIEP, deep inferior epigastric perforator.*
**P < 0.05. **P < 0.005. ***P < 0.001.*

95%CI 9.32 to 28.53, p < 0.001). In addition, "Psychosocial well-being" significantly improved in patients with a bilateral procedure at 5 years (β 0.20, 95% CI -34.31 to -2.90, p = 0.02). No factors were significantly associated with "Physical well-being" at 5 years.

Comparisons of BREAST-Q scores among operative procedures in each year are shown in **Figure 2**. Mastectomy scored significantly lower than TE/Imp and DIEP for "Satisfaction with breasts" and "Psychosocial well-being" (both p < 0.001) at 1 year (all p < 0.001; **Figures 2A, B**) and 5 years (all p < 0.001, except p = 0.007 vs. DIEP for "Satisfaction with breasts"; **Figures 2D, E**). In addition, at 5 years, DIEP scored significantly higher than TE/Imp for "Satisfaction with breasts" (p < 0.001) (**Figure 2D**). Detailed results are shown in **Table S1**.

Comparisons of BREAST-Q scores between 1- and 5-year follow-up evaluations for each operative procedure are shown in **Figure 3**. Scores at 5 years were significantly lower than those at 1 year for "Satisfaction with breasts" for all three procedures (mastectomy only, p = 0.012; TE/Imp p < 0.001; DIEP, p < 0.001; **Figures 3A, D, G**) and for "Physical well-being" for two procedures (TE/Imp, p = 0.007; DIEP, p = 0.008; **Figures 3E, H**). Detailed results are shown in **Table S2**.

## DISCUSSION

In this study, general and aesthetic satisfaction with breast operations including reconstruction were investigated at 1 and 5 years postoperatively in Japanese women. The main finding was that the type of operation was significantly associated with HRQoL-related domains of BREAST-Q at both 1 and 5 years in multivariate analysis. Over time, all surgical procedures had lower scores for "Satisfaction with breasts", but "Psychosocial well-being" was maintained and "Physical well-being" improved after TE/Imp and DIEP. "Satisfaction with breasts" and "Psychosocial well-being" were lowest for mastectomy only at 1 and 5 years, and "Satisfaction with breasts" at 5 years was best after DIEP.

To our knowledge, there have been few long-term studies of HRQoL after breast surgery. Long-term evaluations of 5 years or more that have been performed are shown in **Table 3** (32, 33, 35, 36). In the current study, the response rate and score for "Satisfaction with breasts" declined from postoperative year 1 to year 5. The lower response rate is consistent with previous studies showing a decline in response rate for PROs over time, as patients lose interest in the aesthetic impact of breast surgery (37–41). A lower score at a later time has also been found previously (42, 43) and is due to patients becoming used to the results of reconstruction over time. Thus, the time after the operation is an important factor associated with HRQoL.

Among patient factors, higher BMI was significantly negatively associated with "Satisfaction with breasts" at 1-year postoperatively, but not at 5 years. This is consistent with several reports showing that high BMI is an independent risk factor for lower satisfaction (44–46). However, most of these studies did not obtain baseline data using the preoperative module of BREAST-Q. Previous reports

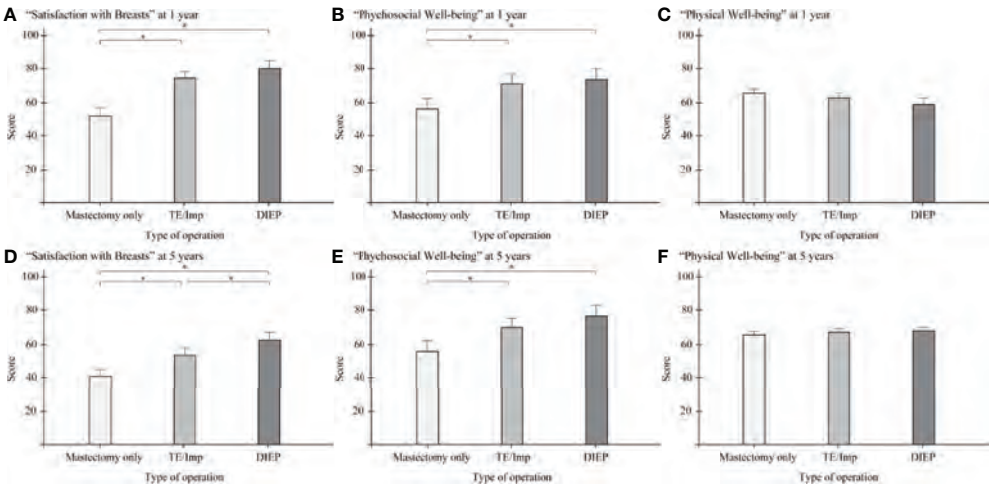



**FIGURE 2** | Comparison of BREAST-Q scores among operative procedures in each year, with 95% confidence intervals. **(A)** "Satisfaction with breasts" at 1 year; **(B)** "Psychosocial well-being" at 1 year; **(C)** "Physical well-being" at 1 year; **(D)** "Satisfaction with breasts" at 5 years; **(E)** "Psychosocial well-being" at 5 years; **(F)** "Physical well-being" at 5 years. TE/Imp, tissue expander/implant; DIEP, deep inferior epigastric perforator. *P < 0.05.

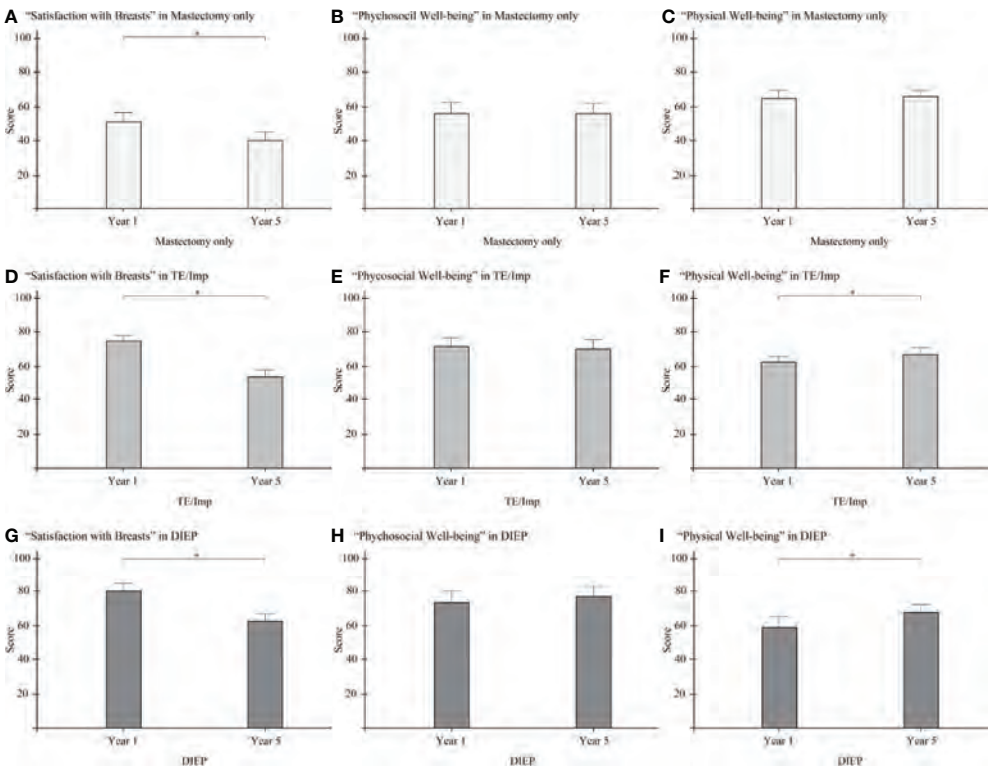



**FIGURE 3** | Comparison of BREAST-Q scores in 1- and 5-year follow-up evaluations for three operative procedures, with 95% confidence intervals. **(A)** "Satisfaction with breasts" in mastectomy only; **(B)** "Psychosocial well-being" in mastectomy only; **(C)** "Physical well-being" in mastectomy only; **(D)** "Satisfaction with breasts" in TE/Imp; **(E)** "Psychosocial well-being" in TE/Imp; **(F)** "Physical well-being" in TE/Imp; **(G)** "Satisfaction with breasts" in DIEP; **(H)** "Psychosocial well-being" in DIEP; **(I)** "Physical well-being" in DIEP. TE/Imp, tissue expander/implant; DIEP, deep inferior epigastric perforator. *P < 0.05.

**TABLE 3 |** Comparison of long-term breast reconstruction studies using BREAST-Q.

| Reference | Patient Base | Number of Patients | BREAST-Q Postop Follow-up Period | Scales | Protective factors | Risk factors |
|---|---|---|---|---|---|---|
| Hu et al. (32) | TE/Imp and TRAM | 219 | 6.5 years* | Satisfaction with breasts | TRAM | TE/Imp; early postoperative period |
| Ledibabari et al. (33) | Mammoplasty | 70 | 6 years* | Satisfaction with breasts | None | Obesity |
| Ticha et al. (34) | Implant-based reconstruction, abdominal-based autologous reconstruction, and combined reconstruction (with implant and LD flap or implant and TDAP flap) | 110 | 5 years | Satisfaction with breasts | Abdominal-based autologous reconstruction | None |
| | | | | Psychosocial well-being | Abdominal-based autologous reconstruction | None |
| | | | | Physical well-being | Abdominal-based autologous reconstruction | None |
| Dominici et al. (35) | Mastectomy, radiotherapy, and autologous flap | 290 | 5.8 years** | Satisfaction with Breasts | None | TE/Imp |
| | | | | Psychosocial well-being | None | None |
| | | | | Physical well-being | None | Complex reconstruction (vs. autologous) |

*TE/Imp, tissue expander/implant; DIEP, deep inferior epigastric perforator; TRAM, transverse rectus abdominis myocutaneous; LD, latissimus dorsi flap; TDAP, thoracodorsal artery perforator flap.*
**Mean; **Median.*

have also shown that obese patients tend to have higher rates of postoperative complications. However, in the current study, higher BMI at 5 years was not a risk factor, which suggests that these complications had resolved or that patients had become used to their postoperative status.

Psychotic/neurological medical history or medication was found to be a significant risk factor that lowers "Physical well-being" at 1 year after breast surgery. The questions in the "Physical well-being" domain are related to physical problems, including pain in the chest, back, abdomen or skin. Among psychological factors, preoperative levels of depression, anxiety, and psychological vulnerability to aberrant pain perception have been reported to be significantly associated with greater postoperative pain intensity, which may decrease physical morbidity (47–51). However, in a previous study, we found no significant association of psychotic/neurological medical history or medication with postoperative pain at one year after breast surgery in a similar cohort of Japanese patients to that in the current study (52). Thus, more psychiatrically oriented pain such as chronic postsurgical pain (CPSP) may have a negative effect on "Physical well-being" of patients (53).

A bilateral procedure was significantly associated with "Psychosocial well-being" at 5 years after breast surgery. Several studies focusing on bilateral breast operations have concluded that "Psychosocial well-being" after surgery significantly improves compared to the preoperative level (54, 55). These findings suggest that patients who underwent bilateral reconstruction were more satisfied due to improved symmetry and a superior aesthetic appearance.

Age was not found to be a significant factor associated with HRQoL among breast cancer survivors in the current study. However, this is still controversial because some reports indicate that implant and autogenous tissue techniques are associated with aging processes that can affect aesthetic appearance (56–60), whereas other studies did not find significant age-related differences using BREAST-Q (61–64). Reconstructive surgeons may avoid autologous reconstruction in older women due to complications following longer anesthetic times, but our results indicate that autologous procedures can be viable choices in older patients, given that age is not associated with greater risks and that autologous reconstruction in this population still achieves high HRQoL.

In this study, we focused on general and aesthetic well-being after breast surgery. Postoperative complications such as lymphedema, AWS, and fatigue can lower HRQoL, but intervention through rehabilitation can improve satisfaction (6–8). Risk factors for each complication have been described (65–68) and there are also several predictive methods for the complications. For example, de Sire et al. found that measuring the upper limb volume using a three-dimensional laser scanner was a reliable way to diagnose breast cancer-related lymphedema (69), and Nevola Teixeira et al. established a self-assessment questionnaire for AWS (70). A combination of BREAST-Q and these diagnostic methods is a promising approach for evaluation of complications.

The main strength of the study is the long-term evaluation of PROs for breast reconstruction. There are several limitations in the study. The main limitation was the response rates of 68.8% at 1 year and 63.9% at 5 years. However, these rates are similar to those in previous reports (71–73). Patients were followed for up to 5 years, but with such a long study period some could not be contacted or may have died, and were lost to follow up. It is also possible that there was a non-response bias, since patients who are still thinking about the complications of their breast reconstruction are more

likely to respond to a questionnaire. We also did not examine the baseline status of the patients in terms of their well-being and satisfaction, and we were unable to assess changes in BMI in the postoperative period, which may influence patient satisfaction. However, in a retrospective study, Applebaum et al. found no significant change in BMI over time following implant-based or autologous breast reconstruction (74). The current study was also restricted to a single center with a relatively homogeneous patient population and evaluation, which could lead to potential selection bias. Finally, it was difficult to control for variability in operative techniques of surgeons and management of postoperative complications in statistical analysis.

In conclusion, the BREAST-Q score for "Physical well-being" was maintained at 5 years after breast reconstruction, and breast reconstruction procedures were better than mastectomy for "Satisfaction with breasts" and "Psychosocial well-being". DIEP had the best scores among the three procedures at 5 years postoperatively. Thus, autologous reconstruction using a DIEP flap is recommended in terms of long-term satisfaction after breast surgery. These results are clinically useful for the choice of operative method by surgeons and patients. However, factors such as ethnic and regional differences may affect the results in other cohorts, and further research is required to promote better satisfaction with HRQoL after breast reconstruction.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Kyoto Prefectural University of Medicine, IRBMED Number ERB-C-563-1. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

MS and YS contributed to the conceptualization, methodology, investigation, and revision of the manuscript. MS wrote the original draft. TK and NI contributed to the collection of patient data, the investigation, and revision of the manuscript. IT and NM contributed to the revise of the article.

## FUNDING

Costs related to statistical analysis and manuscript publication were funded through the department of Plastic and Reconstructive Surgery, Kyoto Prefectural University of Medicine.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.815498/full#supplementary-material

## REFERENCES

1. Heer E, Harper A, Escandor N, Sung H, McCormack V, Fidler-Benaoudia MM. Global Burden and Trends in Premenopausal and Postmenopausal Breast Cancer: A Population-Based Study. *Lancet Glob Health* (2020) 8(8): e1027–37. doi: 10.1016/s2214-109x(20)30215-1
2. Nardin S, Mora E, Varughese FM, D'Avanzo F, Vachanaram AR, Rossi V, et al. Breast Cancer Survivorship, Quality of Life, and Late Toxicities. *Front Oncol* (2020) 10:864. doi: 10.3389/fonc.2020.00864
3. Invernizzi M, Kim J, Fusco N. Editorial: Quality of Life in Breast Cancer Patients and Survivors. *Front Oncol* (2020) 10:620574. doi: 10.3389/fonc.2020.620574
4. Nakamura K, Okada E, Ukawa S, Hirata M, Nagai A, Yamagata Z, et al. Characteristics and Prognosis of Japanese Female Breast Cancer Patients: The BioBank Japan Project. *J Epidemiol* (2017) 27(3S):S58–64. doi: 10.1016/j.je.2016.12.009
5. Saika K, Sobue T. Time Trends in Breast Cancer Screening Rates in the OECD Countries. *Jpn J Clin Oncol* (2011) 41(4):591–2. doi: 10.1093/jjco/hyr044
6. Pappalardo M, Starnoni M, Franceschini G, Baccarani A, De Santis G. Breast Cancer-Related Lymphedema: Recent Updates on Diagnosis, Severity and Available Treatments. *J Pers Med* (2021) 11(5):402. doi: 10.3390/jpm11050402
7. de Sire A, Losco L, Cisari C, Gennari A, Boldorini R, Fusco N, et al. Axillary Web Syndrome in Women After Breast Cancer Surgery Referred to an Oncological Rehabilitation Unit: Which Are the Main Risk Factors? A Retrospective Case-Control Study. *Eur Rev Med Pharmacol Sci* (2020) 24 (15):8028–35. doi: 10.26355/eurrev_202008_22486
8. Invernizzi M, de Sire A, Lippi L, Venetis K, Sajjadi E, Gimigliano F, et al. Impact of Rehabilitation on Breast Cancer Related Fatigue: A Pilot Study. *Front Oncol* (2020) 10:556718. doi: 10.3389/fonc.2020.556718
9. Dean C, Chetty U, Forrest AP. Effects of Immediate Breast Reconstruction on Psychosocial Morbidity After Mastectomy. *Lancet* (1983) 1(8322):459–62. doi: 10.1016/s0140-6736(83)91452-6
10. Heil J, Czink E, Golatta M, Schott S, Hof H, Jenetzky E, et al. Change of Aesthetic and Functional Outcome Over Time and Their Relationship to Quality of Life After Breast Conserving Therapy. *Eur J Surg Oncol* (2011) 37 (2):116–21. doi: 10.1016/j.ejso.2010.11.007
11. Waljee JF, Hu ES, Ubel PA, Smith DM, Newman LA, Alderman AK. Effect of Esthetic Outcome After Breast-Conserving Surgery on Psychosocial Functioning and Quality of Life. *J Clin Oncol* (2008) 26(20):3331–7. doi: 10.1200/JCO.2007.13.1375
12. Davies CF, Macefield R, Avery K, Blazeby JM, Potter S. Patient-Reported Outcome Measures for Post-Mastectomy Breast Reconstruction: A Systematic Review of Development and Measurement Properties. *Ann Surg Oncol* (2021) 28(1):386–404. doi: 10.1245/s10434-020-08736-8
13. Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a New Patient-Reported Outcome Measure for Breast Surgery: The BREAST-Q. *Plast Reconstr Surg* (2009) 124(2):345–53. doi: 10.1097/PRS.0b013e3181aee807
14. Cano SJ, Klassen AF, Scott AM, Cordeiro PG, Pusic AL. The BREAST-Q: Further Validation in Independent Clinical Samples. *Plast Reconstr Surg* (2012) 129(2):293–302. doi: 10.1097/PRS.0b013e31823aec6b
15. Cohen WA, Mundy LR, Ballard TN, Klassen A, Cano SJ, Browne J, et al. The BREAST-Q in Surgical Research: A Review of the Literature 2009-2015. *J Plast Reconstr Aesthet Surg* (2016) 69(2):149–62. doi: 10.1016/j.bjps.2015.11.013
16. Stolpner I, Heil J, Feißt M, Karsten MM, Weber WP, Blohmer JU, et al. Clinical Validation of the BREAST-Q Breast-Conserving Therapy Module. *Ann Surg Oncol* (2019) 26(9):2759–67. doi: 10.1245/s10434-019-07456-y

17. Nano MT, Gill PG, Kollias J, Bochner MA, Malycha P, Winefield HR. Psychological Impact and Cosmetic Outcome of Surgical Breast Cancer Strategies. *ANZ J Surg* (2005) 75(11):940–7. doi: 10.1111/j.1445-2197.2005.03517.x
18. Saulis AS, Mustoe TA, Fine NA. A Retrospective Analysis of Patient Satisfaction With Immediate Postmastectomy Breast Reconstruction: Comparison of Three Common Procedures. *Plast Reconstr Surg* (2007) 119 (6):1669–76. doi: 10.1097/01.prs.0000258827.21635.84
19. Mosahebi A, Ramakrishnan V, Gittos M, Collier J. Aesthetic Outcome of Different Techniques of Reconstruction Following Nipple-Areola-Preserving Envelope Mastectomy With Immediate Reconstruction. *Plast Reconstr Surg* (2007) 119(3):796–803. doi: 10.1097/01.prs.0000251999.52374.09
20. Tykkä E, Asko-Seljavaara S, Hietanen H. Patient Satisfaction With Delayed Breast Reconstruction: A Prospective Study. *Ann Plast Surg* (2002) 49(3):258–63. doi: 10.1097/01.SAP.0000015487.09561.62
21. Tykkä E, Asko-Seljavaara S, Hietanen H. Patients' Satisfaction With Breast Reconstruction and Reduction Mammaplasty. *Scand J Plast Reconstr Surg Handb Surg* (2001) 35(4):399–405. doi: 10.1080/028443101317149363
22. Kovacs L, Papadopulos NA, Ammar SA, Klöppel M, Herschbach P, Heinrich G, et al. Clinical Outcome and Patients' Satisfaction After Simultaneous Bilateral Breast Reconstruction With Free Transverse Rectus Abdominis Muscle (TRAM) Flap. *Ann Plast Surg* (2004) 53(3):199–204. doi: 10.1097/01.sap.0000120525.86997.52
23. Ramon Y, Ullmann Y, Moscona R, Ofiram E, Tamir A, Har-Shai Y, et al. Aesthetic Results and Patient Satisfaction With Immediate Breast Reconstruction Using Tissue Expansion: A Follow-Up Study. *Plast Reconstr Surg* (1997) 99(3):686–91. doi: 10.1097/00006534-199703000-00013
24. Simon AM, Bouwense CL, McMillan S, Lamb S, Hammond DC. Comparison of Unipedicled and Bipedicled TRAM Flap Breast Reconstructions: Assessment of Physical Function and Patient Satisfaction. *Plast Reconstr Surg* (2004) 113(1):136–40. doi: 10.1097/01.PRS.0000095939.19970.D5
25. Moscona RA, Holander L, Or D, Fodor L. Patient Satisfaction and Aesthetic Results After Pedicled Transverse Rectus Abdominis Muscle Flap for Breast Reconstruction. *Ann Surg Oncol* (2006) 13(12):1739–46. doi: 10.1245/s10434-006-9096-7
26. Stolpner I, Heil J, Riedel F, Wallwiener M, Schäfgen B, Feißt M, et al. Long-Term Patient Satisfaction and Quality of Life After Breast-Conserving Therapy: A Prospective Study Using the BREAST-Q. *Ann Surg Oncol* (2021) 28:8742–51. doi: 10.1245/s10434-021-10377-4
27. Lantz PM, Janz NK, Fagerlin A, Schwartz K, Liu L, Lakhani I, et al. Satisfaction With Surgery Outcomes and the Decision Process in a Population-Based Sample of Women With Breast Cancer. *Health Serv Res* (2005) 40(3):745–67. doi: 10.1111/j.1475-6773.2005.00383.x
28. Alderman AK, Wilkins EG, Lowery JC, Kim M, Davis JA. Determinants of Patient Satisfaction in Postmastectomy Breast Reconstruction. *Plast Reconstr Surg* (2000) 106(4):769–76. doi: 10.1097/00006534-200009040-00003
29. Howes BH, Watson DI, Xu C, Fosh B, Canepa M, Dean NR. Quality of Life Following Total Mastectomy With and Without Reconstruction Versus Breast-Conserving Surgery for Breast Cancer: A Case-Controlled Cohort Study. *J Plast Reconstr Aesthet Surg* (2016) 69(9):1184–91. doi: 10.1016/j.bjps.2016.06.004
30. Shiraishi M, Sowa Y, Inafuku N. Long-Term Survey of Sexual Well-Being After Breast Reconstruction Using the BREAST-Q in the Japanese Population. *Asian J Surg*, S1015–9584(22)00108-7. doi: 10.1016/j.asjsur.2022.02.007
31. Saiga M, Taira N, Kimata Y, Watanabe S, Mukai Y, Shimozuma K, et al. Development of a Japanese Version of the BREAST-Q and the Traditional Psychometric Test of the Mastectomy Module for the Assessment of HRQOL and Patient Satisfaction Following Breast Surgery. *Breast Cancer* (2017) 24 (2):288–98. doi: 10.1007/s12282-016-0703-6
32. Hu ES, Pusic AL, Waljee JF, Kuhn L, Hawley ST, Wilkins E, et al. Patient-Reported Aesthetic Satisfaction With Breast Reconstruction During the Long-Term Survivorship Period. *Plast Reconstr Surg* (2009) 124(1):1–8. doi: 10.1097/PRS.0b013e3181ab10b2
33. Ngaage LM, Bai J, Gebran S, Elegbede A, Ihenatu C, Nam AJ, et al. A 12-Year Review of Patient-Reported Outcomes After Reduction Mammoplasty in Patients With High Body Mass Index. *Med (Baltimore)* (2019) 98(25): e16055. doi: 10.1097/MD.0000000000016055
34. Ticha P, Mestak O, Wu M, Bujda M, Sukop A. Patient-Reported Outcomes of Three Different Types of Breast Reconstruction With Correlation to the Clinical Data 5 Years Postoperatively. *Aesthetic Plast Surg* (2020) 44 (6):2021–9. doi: 10.1007/s00266-020-01926-5
35. Dominici L, Hu J, Zheng Y, Kim HJ, King TA, Ruddy KJ, et al. Association of Local Therapy With Quality-Of-Life Outcomes in Young Women With Breast Cancer. *JAMA Surg* (2021) 156(10):e213758. doi: 10.1001/jamasurg.2021.3758
36. Ticha P, Wu M, Mestak O, Sukop A. Evaluation of the Number of Follow-Up Surgical Procedures and Time Required for Delayed Breast Reconstruction by Clinical Risk Factors, Type of Oncological Therapy, and Reconstruction Approach. *Aesthetic Plast Surg* (2021) 46(1):71–82. doi: 10.1007/s00266-021-02580-1
37. Reinholdsson J, Kraus-Schmitz J, Forssblad M, Edman G, Byttner M, Stålman A. A non-Response Analysis of 2-Year Data in the Swedish Knee Ligament Register. *Knee Surg Sports Traumatol Arthrosc* (2017) 25(8):2481–7. doi: 10.1007/s00167-015-3969-x
38. Juto H, Gärtner Nilsson M, Möller M, Wennergren D, Morberg P. Evaluating non-Responders of a Survey in the Swedish Fracture Register: No Indication of Different Functional Result. *BMC Musculoskelet Disord* (2017) 18(1):278. doi: 10.1186/s12891-017-1634-x
39. Patel J, Lee JH, Li Z, SooHoo NF, Bozic K, Huddleston JI3rd. Predictors of Low Patient-Reported Outcomes Response Rates in the California Joint Replacement Registry. *J Arthroplasty* (2015) 30(12):2071–5. doi: 10.1016/j.arth.2015.06.029
40. Wang K, Eftang CN, Jakobsen RB, Årøen A. Review of Response Rates Over Time in Registry-Based Studies Using Patient-Reported Outcome Measures. *BMJ Open* (2020) 10(8):e030808. doi: 10.1136/bmjopen-2019-030808
41. Liu LQ, Branford OA, Mehigan S. BREAST-Q Measurement of the Patient Perspective in Oncoplastic Breast Surgery: A Systematic Review. *Plast Reconstr Surg Glob Open* (2018) 6(8):e1904. doi: 10.1097/GOX.0000000000001904
42. Flanagan MR, Zabor EC, Romanoff A, Fuzesi S, Stempel M, Mehrara BJ, et al. A Comparison of Patient-Reported Outcomes After Breast-Conserving Surgery and Mastectomy With Implant Breast Reconstruction. *Ann Surg Oncol* (2019) 26(10):3133–40. doi: 10.1245/s10434-019-07548-9
43. Santosa KB, Qi J, Kim HM, Hamill JB, Wilkins EG, Pusic AL. Long-Term Patient-Reported Outcomes in Postmastectomy Breast Reconstruction. *JAMA Surg* (2018) 153(10):891–9. doi: 10.1001/jamasurg.2018.1677
44. Atisha DM, Rushing CN, Samsa GP, Locklear TD, Cox CE, Shelley Hwang E, et al. A National Snapshot of Satisfaction With Breast Cancer Procedures. *Ann Surg Oncol* (2015) 22(2):361–9. doi: 10.1245/s10434-014-4246-9
45. O'Connell RL, DiMicco R, Khabra K, O'Flynn EA, deSouza N, Roche N, et al. Initial Experience of the BREAST-Q Breast-Conserving Therapy Module. *Breast Cancer Res Treat* (2016) 160(1):79–89. doi: 10.1007/s10549-016-3966-x
46. Nelson JA, Sobti N, Patel A, Matros E, McCarthy CM, Dayan JH, et al. The Impact of Obesity on Patient-Reported Outcomes Following Autologous Breast Reconstruction. *Ann Surg Oncol* (2020) 27(6):1877–88. doi: 10.1245/s10434-019-08073-5
47. Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of Postoperative Pain and Analgesic Consumption: A Qualitative Systematic Review. *Anesthesiology* (2009) 111(3):657–77. doi: 10.1097/ALN.0b013e3181aae87a
48. Kulkarni AR, Pusic AL, Hamill JB, Kim HM, Qi J, Wilkins EG, et al. Factors Associated With Acute Postoperative Pain Following Breast Reconstruction. *JPRAS Open* (2017) 11:1–13. doi: 10.1016/j.jpra.2016.08.005
49. Munafò MR, Stevenson J. Anxiety and Surgical Recovery. Reinterpreting the Literature. *J Psychosom Res* (2001) 51(4):589–96. doi: 10.1016/s0022-3999(01)00258-6
50. Khan RS, Ahmed K, Blakeway E, Skapinakis P, Nihoyannopoulos L, Macleod K, et al. Catastrophizing: A Predictive Factor for Postoperative Pain. *Am J Surg* (2011) 201(1):122–31. doi: 10.1016/j.amjsurg.2010.02.007
51. Pinto PR, McIntyre T, Almeida A, Araújo-Soares V. The Mediating Role of Pain Catastrophizing in the Relationship Between Presurgical Anxiety and Acute Postsurgical Pain After Hysterectomy. *Pain* (2012) 153(1):218–26. doi: 10.1016/j.pain.2011.10.020
52. Shiraishi M, Sowa Y, Fujikawa K, Kodama T, Okamoto A, Numajiri T, et al. Factors Associated With Chronic Pain Following Breast Reconstruction in

Japanese Women. *J Plast Surg Handb Surg* (2020) 54(5):317–22. doi: 10.1080/2000656X.2020.1780246
53. Weinrib AZ, Azam MA, Birnie KA, Burns LC, Clarke H, Katz J. The Psychology of Chronic Post-Surgical Pain: New Frontiers in Risk Factor Identification, Prevention and Management. *Br J Pain* (2017) 11(4):169–77. doi: 10.1177/2049463717720636
54. Klapdor R, Weiß C, Kuehnle E, Kohls F, von Ehr J, Philippeit A, et al. Quality of Life After Bilateral and Contralateral Prophylactic Mastectomy With Implant Reconstruction. *Breast Care (Basel)* (2020) 15(5):519–26. doi: 10.1159/000505449
55. Wampler AT, Powelson IA, Homa K, Freed GL. BREAST-Q Outcomes Before and After Bilateral Reduction Mammaplasty. *Plast Reconstr Surg* (2021) 147 (3):382e–90e. doi: 10.1097/PRS.0000000000007605
56. Alderman AK, Kuhn LE, Lowery JC, Wilkins EG. Does Patient Satisfaction With Breast Reconstruction Change Over Time? Two-Year Results of the Michigan Breast Reconstruction Outcomes Study. *J Am Coll Surg* (2007) 204 (1):7–12. doi: 10.1016/j.jamcollsurg.2006.09.022
57. Clough KB, O'Donoghue JM, Fitoussi AD, Nos C, Falcou MC. Prospective Evaluation of Late Cosmetic Results Following Breast Reconstruction: I. Implant Reconstruction. *Plast Reconstr Surg* (2001) 107(7):1702–9. doi: 10.1097/00006534-200106000-00010
58. Clough KB, O'Donoghue JM, Fitoussi AD, Vlastos G, Falcou MC. Prospective Evaluation of Late Cosmetic Results Following Breast Recon- Struction: II. TRAM Flap Reconstruction. *Plast Reconstr Surg* (2001) 107:1710–6. doi: 10.1097/00006534-200106000-00011
59. Spear SL, Onyewu C. Staged Breast Reconstruction With Saline-Filled Implants in the Irradiated Breast: Recent Trends and Therapeutic Implications. *Plast Reconstr Surg* (2000) 105(3):930–42. doi: 10.1097/00006534-200003000-00016
60. Yang B, Li L, Yan W, Chen J, Chen Y, Hu Z, et al. The Type of Breast Reconstruction May Not Influence Patient Satisfaction in the Chinese Population: A Single Institutional Experience. *PloS One* (2015) 10(11): e0142900. doi: 10.1371/journal.pone.0142900
61. Song D, Slater K, Papsdorf M, Van Laeken N, Zhong T, Hazen A, et al. Autologous Breast Reconstruction in Women Older Than 65 Years Versus Women Younger Than 65 Years: A Multi-Center Analysis. *Ann Plast Surg* (2016) 76(2):155–63. doi: 10.1097/SAP.0000000000000527
62. August DA, Wilkins E, Rea T. Breast Reconstruction in Older Women. *Surgery* (1994) 115(6):663–8.
63. Bowman CC, Lennox PA, Clugston PA, Courtemanche DJ. Breast Reconstruction in Older Women: Should Age be an Exclusion Criterion? *Plast Reconstr Surg* (2006) 118(1):16–22. doi: 10.1097/01.prs.0000220473.94654.a4
64. Santosa KB, Qi J, Kim HM, Hamill JB, Pusic AL, Wilkins EG. Effect of Patient Age on Outcomes in Breast Reconstruction: Results From a Multicenter Prospective Study. *J Am Coll Surg* (2016) 223(6):745–54. doi: 10.1016/j.jamcollsurg.2016.09.003
65. Monleon S, Murta-Nascimento C, Bascuas I, Macià F, Duarte E, Belmonte R. Lymphedema Predictor Factors After Breast Cancer Surgery: A Survival Analysis. *Lymphat Res Biol* (2015) 13(4):268–74. doi: 10.1089/lrb.2013.0042
66. Martínez-Jaimez P, Armora Verdú M, Forero CG, Álvarez Salazar S, Fuster Linares P, Monforte Royo C, et al. Breast Cancer-Related Lymphoedema: Risk Factors and Prediction Model. *J Adv Nurs* (2022) 78(3):765–75. doi: 10.1111/jan.15005
67. Tay MRJ, Wong CJ, Aw HZ. Prevalence and Associations of Axillary Web Syndrome in Asian Women After Breast Cancer Surgery Undergoing a Community-Based Cancer Rehabilitation Program. *BMC Cancer* (2021) 21 (1):1019. doi: 10.1186/s12885-021-08762-z
68. de Sire A, Invernizzi M, Lippi L, Cisari C, Özçakar L, Franchignoni F. Blurred Lines Between Axillary Web Syndrome and Mondor's Disease After Breast Cancer Surgery: A Case Report. *Ann Phys Rehabil Med* (2020) 63(4):365–7. doi: 10.1016/j.rehab.2019.04.007
69. de Sire A, Losco L, Cigna E, Lippi L, Gimigliano F, Gennari A, et al. Three-Dimensional Laser Scanning as a Reliable and Reproducible Diagnostic Tool in Breast Cancer Related Lymphedema Rehabilitation: A Proof-of-Principle Study. *Eur Rev Med Pharmacol Sci* (2020) 24(8):4476–85. doi: 10.26355/eurrev_202004_21030
70. Nevola Teixeira LF, Veronesi P, Lohsiriwat V, Luini A, Schorr MC, Garusi C, et al. Axillary Web Syndrome Self-Assessment Questionnaire: Initial Development and Validation. *Breast* (2014) 23(6):836–43. doi: 10.1016/j.breast.2014.09.001
71. García-Solbas S, Lorenzo-Liñán MÁ, Castro-Luna G. Long-Term Quality of Life (BREAST-Q) in Patients With Mastectomy and Breast Reconstruction. *Int J Environ Res Public Health* (2021) 18(18):9707. doi: 10.3390/ijerph18189707
72. Thorarinsson A, Fröjd V, Kölby L, Ljungdal J, Taft C, Mark H. Long-Term Health-Related Quality of Life After Breast Reconstruction: Comparing 4 Different Methods of Reconstruction. *Plast Reconstr Surg Glob Open* (2017) 5 (6):e1316. doi: 10.1097/GOX.0000000000001316
73. Gass JS, Onstad M, Pesek S, Rojas K, Fogarty S, Stuckey A, et al. Breast-Specific Sensuality and Sexual Function in Cancer Survivorship: Does Surgical Modality Matter? *Ann Surg Oncol* (2017) 24(11):3133–40. doi: 10.1245/s10434-017-5905-4
74. Applebaum MA, Miller BT, Lopez J, Doren EL, Laronga C, Smith PD. Change in Body Mass Index After Breast Reconstruction and Associated Complications. *Eplasty* (2015) 15:e43.

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Oncology

REVIEW
published: 25 May 2022
doi: 10.3389/fonc.2022.848485

# Primary Neuroendocrine Tumor of the Breast: Current Understanding and Future Perspectives

*Hongna Sun[1†], Shuang Dai[2†], Junnan Xu[1], Linan Liu[3], Jiaxing Yu[1] and Tao Sun[1*]*

*[1] Department of Medical Oncology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute, Shenyang, China, [2] Department of Medical Oncology, Lung Cancer Center, West China Hospital, Sichuan University, Chengdu, China, [3] Department of Pathology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Shenyang, Liaoning, China*

OPEN ACCESS

***Edited by:***
*Julio de la Torre, Comillas Pontifical University, Spain*

***Reviewed by:***
*Mauro Cives, University of Bari Aldo Moro, Italy*
*Alessandro De Vita, Scientific Institute of Romagna for the Study and Treatment of Tumors (IRCCS), Italy*
*Samia Arifi, Sidi Mohamed Ben Abdellah University, Morocco*

***Correspondence:**
*Tao Sun*
*jianong@126.com*

*[†]These authors have contributed equally to this work*

***Specialty section:***
*This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology*

***Received:*** *04 January 2022*
***Accepted:*** *14 April 2022*
***Published:*** *25 May 2022*

***Citation:***
*Sun H, Dai S, Xu J, Liu L, Yu J and Sun T (2022) Primary Neuroendocrine Tumor of the Breast: Current Understanding and Future Perspectives. Front. Oncol. 12:848485. doi: 10.3389/fonc.2022.848485*

Primary neuroendocrine carcinoma of the breast (NECB) is characterized with heterogeneity, rarity, and poor differentiation, which is probably an underestimated subtype of breast cancer, including small cell NECs and large cell NECs. The diagnostic criteria for NECB have been constantly updated as the disease changes and the understanding increases. According to the latest WHO Classification, primary neuroendocrine neoplasm (NEN) of the breast consists of well-differentiated neuroendocrine tumors (NET), extremely aggressive neuroendocrine carcinomas (NEC) as well as invasive breast cancers of no special type (IBCs-NST) with neuroendocrine differentiation. The accurate diagnosis of NECB remains a challenge for its low incidence, which needs multi-disciplinary methods. For the rarity of the disease, there is a lack of large samples and prospective clinical research. For these invasive tumors, there are no standardized therapeutic guidelines or norms, and the treatment often refers to nonspecific breast cancer. In addition, the prognosis of such patients remains unknown. In 2003, the World Health Organization (WHO) listed NECB as an independent entity for the first time, while few features of NECB were clarified. In this review, it presents the WHO Classification, clinicopathologic characteristics, diagnosis, treatment, and prognosis of these patients. In addition, it summarizes the latest studies on molecular features of NECB, aiming to provide new therapeutic perspectives for the disease.

**Keywords: primary neuroendocrine carcinoma of the breast, neuroendocrine neoplasia, clinicopathologic characteristics, diagnosis, treatment, prognosis, literature review**

## INTRODUCTION

Neuroendocrine neoplasm (NEN) has features distinguished from other solid malignancies. Neuroendocrine cells scatter around the whole body with the dual characteristics of nerve cell-like structure and endocrine cell-like biological activity. As neuroendocrine cells are distributed throughout the whole body, NENs may appear in nearly all organ systems. NEN frequently occurs in the

gastroenteropancreatic system and the bronchopulmonary system (1), and rare primary tumors occur in the skin, thyroid gland, bladder, and larynx (2–4). Primary neuroendocrine carcinoma of the breast (NECB) has characteristics of heterogeneity, rarity, and poor differentiation, and it is an underestimated subtype of breast cancer. Previous studies have reported that the incidence of NECB is variable for the rarity of the disease and the developing diagnostic criteria. In 2003, the World Health Organization (WHO) officially defined NECB as expressing neuroendocrine markers in more than 50% of tumor cells. The WHO Classification of tumors of the breast in 2012 objected to the edition in 2003 and suggested that the diagnosis could be confirmed regardless of the percentage (50% threshold) of tumor cells expressing neuroendocrine biomarkers (5). The latest WHO Classification 2019 unified NEN of the breast with that of other organ systems based on histological features and defined NEN into well-differentiated neuroendocrine tumors (NETs), highly aggressive neuroendocrine carcinomas (NECs), and invasive breast cancers of no special type (IBCs-NST) with neuroendocrine differentiation (6).

At present, there is no conclusion on the histogenesis of the disease. The main clinical features of NECB are breast lump, skin ulceration, bloody nipple discharge, and skin retraction, which are similar to those of IBC-NST. Compared to invasive ductal cancers of no special type (IDCs-NST), NECB is more likely to present systematic metastasis at diagnosis. In addition to clinical features, radiologic characteristics of NECB are nonspecific. Most NECB patients show positive estrogen receptor (ER) and/or progesterone receptor (PR) expression, implying that NECB is part of the luminal-like type (7). There are certain differences among NECB, IBC-NST, and IDC-NST in terms of morphological features and neuroendocrine biomarkers, which contribute to the diagnosis of NECB. Histogenesis and prognosis of NECB are still ill-defined. In addition, there are no standardized therapeutic guidelines or norms for these invasive tumors, and treatment often refers to nonspecific breast cancer reported in case reports and retrospective studies. Surgery remains the primary treatment for IDC-NST followed by taxane-based or anthracycline chemotherapy, endocrine therapy, and targeted therapy according to the receptor status. Given the low prevalence of NECB, knowledge is limited to case reports and small retrospective studies, and the understanding of the clinical features and management of this disease is limited. In this review, we summarize the clinicopathologic characteristics, diagnosis, treatment, and prognosis of these patients, and we elaborate on the molecular features of NECB to provide new therapeutic perspectives.

## WHO CLASSIFICATION

Neuroendocrine differentiation in breast cancer was first described in 1963 (8). In 1977, Cubilla and Woodruff presented a few breast cancer cases with a carcinoid growth pattern and produced the term breast primary carcinoid tumor (9). In 1985, Bussolati et al. demonstrated positive chromogranin A (CgA) expression in the normal mammary parenchyma, offering definitive proof of neuroendocrine (NE) differentiation (10). In 2000, Sapino et al. first proposed the diagnostic criteria for NECB, and they considered breast carcinomas resembling neuroendocrine tumors of the gastrointestinal tract and lungs in morphological features, demonstrating significant expression of neuroendocrine markers [greater than 50%, particularly CgA and synaptophysin (Syn)] (11).

Until 2003, the WHO Classification (the Third Edition) recognized that breast NETs were an independent breast entity (**Table 1**), and NECB was defined by morphological neuroendocrine features similar to those of gastrointestinal/pulmonary NETs. NETs of the breast were defined as tumors of epithelial origin with neuroendocrine marker (CgA and/or Syn) expression in more than 50% of tumor cells. These cancers were classified as large cell carcinomas, small cell/oat cell carcinomas, and solid NECs based on morphological features.

In 2012, the WHO Classification objected to the edition in 2003, indicating that diagnosis could be confirmed regardless of the percentage (50% threshold) of tumor cells expressing neuroendocrine biomarkers (**Table 1**). NECB was regarded as "carcinomas with neuroendocrine features", which was defined by morphological traits resembling gastrointestinal/pulmonary NETs. NENs were classified into three subgroups as follows: well-differentiated NETs (NETs), poorly differentiated/small cell carcinomas (NECs), and invasive carcinomas with neuroendocrine

**TABLE 1** | Summary of different WHO classifications.

| WHO | Terminology | Diagnosis | Subgroups |
|---|---|---|---|
| 2003 | Neuroendocrine tumor | • Morphological features similar to those of NE tumors of both GI tract and lung<br>• Tumors of epithelial origin<br>• Expression of neuroendocrine markers in more than 50% of tumor cells | • Large cell carcinomas<br>• Small cell/oat cell carcinomas<br>• Solid NE carcinomas |
| 2012 | Carcinomas with neuroendocrine features | • Morphological features similar to those of NE tumors of both GI tract and lung<br>• Express NE markers regardless of the percentage (50% threshold) of tumor cells<br>• Include IBCs-NST and special subtypes with NE differentiation | • NET, well differentiated<br>• NEC, poorly differentiated/small cell carcinoma<br>• IBCs with NE differentiation |
| 2019 | Neuroendocrine neoplasm | •>90% NE histological features or NE marker expression<br>• Exclude solid papillary carcinoma and hypercellular subtype of mucinous carcinoma | • NET, well differentiated<br>• NEC, poorly differentiated (small cell NECs; large cell NECs) |
| | IBCs-NST with neuroendocrine features | •≤90% NE histological features or NE marker expression 10-90%: mixed invasive (NST or other special type) and NECs <10%: invasive NST or other special types commented on the focal NE pattern | |

differentiation. The third group included IBC-NST and special subtypes with neuroendocrine differentiation (solid papillary carcinoma and mucinous carcinoma with neuroendocrine differentiation). However, this edition had small cell NEC but not large cell. The NET and NEC groups presented similar morphological traits as their gastrointestinal/pulmonary counterparts (5).

In 2019, the WHO Classification in the Fifth Edition (**Table 1**) unified NECB with NEN of other organ systems based on histological features to decrease confusion and inconsistencies in classifications, terminology, histologic grading criteria, and TNM staging. Within this framework, the terminology neuroendocrine neoplasms was introduced, including tumors with prominent neuroendocrine differentiation (presence of histologic neuroendocrine features in more than 90% of the tumor cells), and NEN was defined as NET when well differentiated and NEC when poorly differentiated. NEC was further divided into small-cell NECs and large-cell NECs. Furthermore, solid papillary carcinoma and the hypercellular subtype of mucinous carcinoma were excluded. Breast NETs were graded on the basis of the Nottingham grading system, which comprehensively evaluates the proportion of glandular tube formation, nuclear pleomorphism, and mitotic count in invasive breasts, with the quantity of mitoses continuing to be the main parameter in grading systems (6). In addition, if neuroendocrine biomarker expression or histological features make up ≤90% of the tumor area, it is defined as an IBC-NST with neuroendocrine features. When cancers have a 10–90% NEN pattern, the terminology of mixed invasive (NST or other special type) or NEC may be used, and the NEC percentage should be reported. Cancers with <10% NEN pattern should be classified as NST or other special types with an option to describe the focal specialized neuroendocrine pattern in the report comment.

## EPIDEMIOLOGY AND CLINICAL FEATURES

The changes in classification and different morphological and immunohistochemical criteria for the diagnosis of NECB from 2003 to 2019 result in a lack of uniformity in the terminology and definition of NECs, thereby hindering an accurate assessment of the incidence of NECB. Accordingly, the reported morbidity is extremely variable, ranging from 0.1% to 19.5% (12, 13). Wang et al. analyzed 381,644 cases of breast cancer from the database of surveillance, epidemiology, and end results (SEER). The results showed that according to the WHO diagnostic criteria of 2003, only 0.1% of breast cancer is NECB, which is lower than the 2–5% reported by the WHO in 2012 (5), suggesting that NECB may be underestimated because immunohistochemical (IHC) examination for neuroendocrine biomarkers is not routinely performed and cytomorphologic evaluation underestimates neuroendocrine differentiation. Therefore, it is difficult to confirm the true incidence of NECB (14).

NECB is a particular histologic subtype of breast cancer with similar morphological characteristics to gastrointestinal/lung NETs while displaying some degree of heterogeneity, including certain features that are usually difficult to identify from IBC-NST. Therefore, NECB may be misdiagnosed as metastatic breast cancer, carcinomas of IDC-NST, or breast carcinoma with neuroendocrine differentiation.

As the incidence of NECB is low, there is limited knowledge about the specific clinical characteristics of NECB. Most of the data comes from case reports and retrospective studies. The clinical feature of NECB is mainly characterized by a solitary breast lump, probably accompanied by skin ulceration, bloody nipple discharge, skin retraction, palpable axillary mass, and breast discomfort (15). Some people may have complications such as bone pain, respiratory symptoms, abnormal liver function, hematuria, and neuralgia caused by metastasis. While some people have no symptoms, they occasionally discover the disease due to routine mammographic screening. A few patients may suffer from carcinoid syndrome or hormonal hypersecretion. Patient age at diagnosis is mainly between the fifth and seventh decade of life (majority aged >60 years), ranging from 26 to 99 years, and most patients are postmenopausal women with higher clinical stage and histologic grade. However, few NECB patients are men (12, 15, 16). In addition, a previous study has reported one 13-year-old NECB patient (17). Several patients have a history of contralateral or ipsilateral invasive carcinoma of no special type with a tumor size ranging from 0.6 to 18.0 cm (mean: 2.3–3.7 cm), and approximately 40% of NECB has axillary lymph nodal metastasis at diagnosis (15, 16, 18, 19). Compared to IDC-NST, NECB patients are more likely to present systematic metastasis at initial diagnosis, and the most common metastatic sites are bone, liver, lungs, brain, bone marrow, and pleura, and several cases involve skin (18, 20–22). In addition, Kawasaki et al. reported peculiar endovascular spread (23).

There is limited understanding of the radiological features of NECB, and its radiological characteristics are nonspecific. Some studies have reported that NECB often exhibits the following characteristics: as a round, oval, or lobular mass with nonspiculated margins; a sharply circumscribed high-density mass on mammography; a hypoechoic solid mass with indistinct margins, which increases vascularity; and no enhanced posterior echo or a cystic component on breast sonograms (15, 24). Calcifications in NECB are uncommon in comparison with occurrence in invasive breast cancer (15). Magnetic resonance imaging has suggested an irregular mass with ill-defined margins, washout kinetics, and a marginal or heterogeneous internal enhancement pattern (15). In addition, PET-CT with 68 gallium-labelled somatostatin analogues can be used in well-differentiated NECB. 18-Fluorodeoxyglucose (FDG) PET-CT can be performed in poorly differentiated NECB or small cell carcinomas with high metabolic activity (25, 26). It is imperative to differentiate primary NECB from metastatic disease to the breast because it is common for metastatic neuroendocrine tumors to occur from other sites to the breast. Metastasis from other primary sites to the breast can be excluded by suitable methods, such as chest, abdominal, and pelvic computed tomography scans.

The diagnosis of NECB is based on morphological features and neuroendocrine biomarkers, and a biopsy is necessary for a definite diagnosis. Fine-needle aspiration (FNA) cytology may be

inadequate for the diagnosis of NECB as the cytological features of NECB are parallel to those of intraductal papilloma and IDCs. Furthermore, the findings of FNA can be misinterpreted as adenocarcinoma (24). Therefore, the diagnosis is established by imaging-guided (ultrasound, stereotactic, or MRI guidance) core needle biopsy or specimens after surgery. Differential diagnoses include but are not limited to neuroendocrine tumors metastatic to the breast, lymphoma, Merkel cell carcinoma, and melanoma (27). The latest WHO diagnostic criteria for NECB stress the obligation to exclude the probability of metastatic neuroendocrine tumors from other organ systems because ≥97% of all neuroendocrine carcinomas originate from the gastrointestinal tract or lungs (1). It is not easy to differentiate these tumors in some situations, but the appearance of an associated ductal carcinoma component detected by histology is effective evidence of primary NECB (6, 28, 29).

## HISTOGENESIS AND HISTOPATHOLOGY

At present, the histogenesis of NECB is still unclear. Some investigators have proposed that NECB does not originate from pre-existing and/or hyperplastic neuroendocrine cells but instead originates from differentiation events in breast cancer because they could not detect neuroendocrine cells in breast tissues (30). In contrast, Tomonori et al. demonstrated that benign neuroendocrine cells appear in the background of breast parenchyma with NECB and that they are arranged in isolated/scattered, clustered, and circumferential patterns, implying that neuroendocrine cell proliferation may be related to a precancerous state in the histogenesis of NECB (31).

NECB has clinical and radiologic characteristics that are difficult to distinguish from common types of breast cancers. Only approximately 33% of NECB patients can be diagnosed by morphology (32, 33). Consequently, the diagnosis of NECB is made by histology and IHC staining of neuroendocrine markers (**Figure 1**), which plays a critical role in improving the diagnostic rate of NECB. NECB is supported by the appearance of neuro-secretory granules and diffuse (more than 50%), uniform immunoreactivity for neuroendocrine biomarkers. Generally, NECB lesions vary from infiltrative mass lesions to well-circumscribed nodules, and some may have a focal hemorrhage with most tan and firm tumors (32). Histologically, low- or intermediate-grade invasive primary breast NETs are morphologically indistinguishable from their counterparts in the pulmonary region. Morphologically, the WHO definition indicates that breast NET consists of dense cellular solid nests and/or trabeculae of tumor cells in spindled, plasmacytoid, and polygonal shapes with eosinophilic and granular or clear cytoplasm separated by delicate fibrovascular stroma, rosettes, and peripheral palisading (6, 32). Although these tumors have similar cytological features, they may have an *in-situ* component to indicate a mammary gland origin. High Nottingham histologic grade NECB includes small cell NEC and large cell NEC. Small cell NEC accounts for approximately 0.1% of all breast cancers and 3–10% of extrapulmonary small cell carcinomas. Small cell NEC may be caused by the specific differentiation line of mammary cancer stem cells toward the neuroendocrine/small cell type, which can occur at the *in-situ* stage or later (at the invasive stage), rather than the malignant transformation of specific neuroendocrine cells in the normal breast tissue. Small cell NEC shows an infiltrative growth pattern and is composed of densely packed, reasonably uniform, small, dark hyperchromatic nuclei with a high N:C ratio, nuclear molding, scant cytoplasm, inconspicuous nucleoli, and poorly defined cytoplasmic boundaries (6). Similar to breast NETs, histologic and IHC profiles are challenging to distinguish from their lung counterparts. Thus, the appearance of ductal carcinoma *in situ* (DCIS) and the lack of tumors in other organs on radiologic imaging play vital roles in confirming the diagnosis of small cell NEC as a primary breast tumor. Large cell NEC is an exceedingly rare subtype of NECB. Large cell NEC presents highly pleomorphic nuclei with coarse chromatin and moderate cytoplasm.

The advent of the IHC technique makes it possible to identify the neuroendocrine phenotypes in breast cancer subpopulations by displaying their immunoreactivity to CgA, Syn, neuron-specific enolase (NSE), and CD56, which are usually negative in IBC-NSTs. CgA and Syn are the most sensitive neuroendocrine markers, whereas NSE and CD56 have lower sensitivity and specificity. In addition, some new second-generation neuroendocrine biomarkers, namely, INSM transcriptional repressor 1 (INSM1), ISL LIM homeobox 1 (ISL1) and secretagogin (SECG), have been

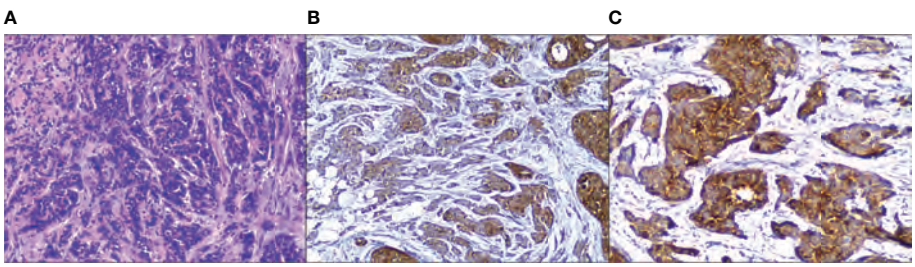



**FIGURE 1** | Pathological findings in primary neuroendocrine carcinoma of the breast. **(A)** H&E stain, tumor cells are composed of dense cellular solid nests, some of which are arranged in alveolar, with round or short spindle cells and eosinophilic cytoplasm. **(B)** Tumor cells show different degrees of positive expression for Chromogranin A on immunohistochemistry. **(C)** Tumor cells show strong and diffuse synaptophysin expression. (Hematoxylin-eosin, original magnification ×100 **(A)**; original magnification ×100 **(B, C)**.

introduced in clinical practice. Juhlin et al. compared these three new biomarkers with CgA and Syn, and they found that ISL1, INSM1, and SECG show the same or slightly lower sensitivity as CgA and Syn, confirming that the second-generation neuroendocrine markers present tissue-specific patterns, which are helpful to identify the primary tumor in the analysis of metastasis (34).

As described above, the essential differential diagnosis of NECB is a metastatic NET from the extramammary site. Because NECB and metastatic NEC to the breast show substantial morphologic overlap, differentiation is difficult. Some site-specific lineage markers can help distinguish NECB and metastatic NET, such as GATA3, mammaglobin, GCDFP15, TTF1, CDX2, and PAX8/PAX6. The most specific biomarkers for primary breast tumors are GATA3, mammaglobin, and GCDFP15, which are negative for secondary tumors (29). TTF1-, CDX2-, and PAX8/PAX6-positive cells are expressed at specific sites. Mohanty et al. reported that TTF1 is positive in approximately 70% of lung metastases, CDX2 is positive in 100% of gastrointestinal metastases, and CDX2 is consistently negative in NECB (29). PAX8/PAX6 positivity implies the origination of the gastric pancreas and duodenum. In addition, IHC staining for myoepithelial cells (such as smooth muscle myosin and p63) can aid in differentiating metastatic neuroendocrine neoplasms from *in-situ* carcinoma (29). Regarding the molecular subtype, most NECBs are hormone receptor-positive and human epidermal growth factor receptor 2 (HER-2)-negative, presenting a luminal-like phenotype, and ER may help distinguish the two entities (16, 35). However, ER positivity alone is not sufficient to determine the nature of the breast as it is neither universally expressed in common breast cancers nor specific to breast tumors. For example, metastatic NETs express ER in 13% (29) and 11% (36) of patients. In addition, some researchers have reported ER and PR positivity in pulmonary, pancreatic, small intestinal, and ovarian neuroendocrine tumors. Similarly, GATA3 has been reported in urothelial carcinomas and other tumors, including cutaneous squamous cell carcinomas, renal epithelial tumors, mesotheliomas, and autonomic nervous system tumors (37, 38). Furthermore, it should be noted that strong TTF1 positivity can also be observed in poorly differentiated mammary NETs (29). Either morphology or IHC markers of NECB have an overlap of metastatic tumors. Therefore, a relevant clinical history must be considered when making a definitive diagnosis.

## MOLECULAR FEATURES

There have been relatively few efforts to better characterize the mutational profile and molecular characteristics of NECB due to its rarity and heterogeneity. Here, we provide an overview of molecular alterations reported in NECB cases and provide a summary in **Table 2**. Evidence has demonstrated that NECB has different mutational profiles from other ER-positive and HER2-negative breast cancers with a lower frequency of PIK3CA mutations and a higher mutation rate in other genes. Ang et al. first reported a systematic investigation of activating mutations of NECB in 2014, identifying mutations in 5 of 15 (33%) NECs, including PIK3CA mutation in 20% of NECB and rare mutations in breast cancer (fibroblast growth factor receptor 1 (FGFR1), FGFR4, kinase insert domain receptor (KDR), and HRAS) (35). Caterina et al. showed that the most common mutated genes are GATA3, FOXA1, TBX3, and ARID1A (3/18, 17%; similar to lobular carcinomas), and they reported that there is a low frequency of PIK3CA, AKT1, and CDH1 mutations (2/18, 11%; identical to mucinous carcinomas) as well as no TP53 mutations (39). Although Vijayvergia et al. reported that TP53 is the most common mutation in poorly differentiated NECs, the locations of the primary site are almost always in the gastrointestinal system (41). Another study has shown that in contrast to standard forms of luminal cancers, NECB has a markedly low rate of PIK3CA mutations (7%) and TP53 mutations (7%) (18).

Vranic et al. suggested several potential targets for novel therapies in NECB for the first time, including predicted expression of trophoblast cell-surface antigen 2 (TROP-2), folate receptor 1 (FOLR1), and H3K36Me3 in NECB, which may lead to the development of new targeted therapy drugs for NECB. In addition, these researchers found CCND1 and FGFR gene amplification in isolated cases. However, their study did not discover MGMT hypermethylation, DLL3 expression, or NTRK gene fusions. Furthermore, they reported that no biomarkers

**TABLE 2** | List of molecular alterations in NECB.

| Molecular alterations | Description | Ref. | Sample size |
|---|---|---|---|
| PIK3CA mutations | • Targeted sequencing analysis found three cases (7%) harboring PIK3CA mutations (18) | Lavigne et al. (18) | 42 |
| | • PIK3CA mutations in 20% of NECB and other rare mutations in breast cancer (FGFR1, FGFR4, KDR, HRAS) using a PCR/mass spectroscopy or semiconductor-based sequencing strategy (35) | Ang et al. (35) | 15 |
| | • The most frequently mutated genes were GATA3, FOXA1, TBX3, ARID1A (3/18, 17%), and PIK3CA, AKT1, CDH1 (2/18, 11%) (39). | Marchiò et al. (39) | 18 |
| TP53 mutations | • Targeted sequencing analysis found three cases (7%) harboring TP53 mutations (C277Y, Y220C, and H193R) (18). | Lavigne et al. (18) | 42 |
| | • No TP53 mutations were detected in NECB, enrichment for FOXA1, TBX3, ARID1A mutations (3/18, 17%), and PIK3CA, AKT1, CDH1 (2/18, 11%) (39). | Marchiò et al. (39) | 18 |
| TROP-2, FOLR1, H3K36Me3 | • TROP-2, FOLR1, and H3K36Me3 were three potential targets for novel therapies in NECB, CCND1, and FGFR gene amplification were found in isolated cases (40). | Vranic et al. (40) | 20 |

predict the efficacy of immune checkpoint inhibitors (programmed death-ligand one expression, microsatellite instability, and tumor mutational burden) (40). At present, all approved biomarkers that respond to PD-1/PD-L1 inhibitors have been demonstrated to be negative. The differences among studies are mainly due to the limited number of cases, the extent of genetic testing, and tumor heterogeneity. Although there are differences, these studies still provide helpful information about NECB and help us to find new targets for a more personalized therapy for this rare entity.

## PROGNOSIS

Although the findings about the prognosis of NECB are controversial, most studies have shown that the prognosis of NECB is poor. In the prospective analysis of Rovera et al. (42), NECB had better survival than infiltrating ductal and lobular carcinoma. Nevertheless, Wang et al. (12) and Yang et al. (22) reported opposite results, showing that NECB had worse overall survival (OS) and disease-specific survival (DSS) than IDC-NST. Furthermore, there are similar outcomes in DSS and OS between large cell and small cell NECs. Another study has suggested that patients with NECB have shorter disease-free survival (DFS) than those diagnosed with IDC-NST, but no significant differences were observed in OS (18). When small cell NEC is specific to histologic subsets, it has the worst prognosis.

Previous studies on the prognostic significance of neuroendocrine differentiation in NECB have yielded contrary results due to different diagnostic criteria and the limited number of cases. Lai et al. (14) found that stratification based on the expression level of neuroendocrine biomarkers may provide information related to prognosis, which is conducive to exploring better treatment strategies; they found that NECB tends to be a luminal-like type. Patients with high expression levels of neuroendocrine markers are associated with less invasive clinical parameters (lower histologic grade, less lymph node metastasis, and lower stages), and the prognosis of these patients is better than those with regular expression levels (16). However, some studies have shown that patients with focal neuroendocrine differentiation have worse OS and DFS than those without neuroendocrine differentiation. Giuseppe et al. (43) reported that neuroendocrine differentiation is significantly associated with T4 stage, G2 grade, ER positivity, and PR positivity. Nevertheless, neuroendocrine differentiation does not affect breast cancer prognosis regarding breast cancer-specific survival (33).

In addition, cancer antigen 15-3 has been shown to be remarkably elevated in a patient at baseline and to significantly decrease after treatment, indicating that CA15-3 may be a prognostic factor (44). In most studies, patients with a large tumor size (>20 mm), higher stage, Ki67 > 14%, and hormone receptor-negative status are related to shorter OS (22). When referring to the influences of therapy strategy on the prognosis in NECB, patients who do not have surgery have poor DSS and OS, while those who receive chemotherapy have better DSS and OS in NENs. Wei et al. suggested that compared to conventional chemotherapy, endocrine treatment and radiation treatment show tendency toward survival benefit. However, none of the treatments reached statistical significance in their study, mainly due to the limited number of cases and short-term follow-up (16).

## THERAPY

Multiple studies have shown that compared to IDC-NST, NECB is related to more invasive behavior and has a higher tendency for distant metastasis and local recurrence as well as a worse prognosis. However, given the rarity of NECB, there are currently no randomized controlled trials to compare treatment modalities or combinations of modalities in patients with NECB. Numerous treatments of NECB refer to the norm of ductal carcinoma reported in case reports and retrospective studies with surgery as the first-line therapy followed by taxane-based and/or anthracycline-chemotherapy, endocrine therapy, and targeted therapy according to the receptor status.

Surgery remains an essential method of treatment for early-stage NECB. The selection of surgery method for NECB resembles that for general breast cancer. Surgeons need to consider comprehensive factors, such as age, physical condition, tumor size and location, as well as the ratio of tumor size to breast volume. Of these factors, the size and location of the tumor determine the methods of surgery. There are many available surgical options, including breast-conserving surgery, modified radical mastectomy, breast reconstruction, and total mastectomy.

To date, there is still a lack of evidence for selecting the most effective chemotherapy protocols. Chemotherapy agents can be selected based on the histopathological characteristics of NECB. In general, poorly differentiated, small cell NEC or large cell NEC are treated with platinum/etoposide-containing regimens (45, 46). Taxane-based and/or anthracycline chemotherapy is used for other types of NECB (47). There is little evidence on whether NECB should be treated with neoadjuvant chemotherapy. Sanguinetti et al. treated a solid NECB using neoadjuvant chemotherapy with carboplatin and etoposide, which achieved a stable condition (48). Wei et al. reported that an NECB patient had a significant response after receiving four cycles of TEC (docetaxel, epirubicin, and cyclophosphamide) chemotherapy, resulting in a significant decrease in the Ki-67 proliferation rate from 40% to 10% (47). However, a conclusive recommendation cannot be suggested due to a limited scope of knowledge. Nonetheless, we suggest that patients with a large mass (>5 cm) with a powerful desire to preserve the breast, locally advanced NECB, or inoperable NECB can receive neoadjuvant chemotherapy. Adjuvant chemotherapy should be individualized, taking the biological characteristics and the risk of recurrence of the disease into account. High tumor grade, large tumor size, and lymph node metastases are essential negative prognostic factors for NECB (16).

As described above, studies have shown that the ER and PR in NECB are often highly expressed, presenting a luminal-like

phenotype (16). Furthermore, endocrine therapy has a definitive effect on treating HR-positive breast cancer, indicating that it may be a helpful strategy in treating NECB. Some studies have reported that hormonal therapy combined with other therapy strategies is used to treat NECB when the tumor expresses the appropriate receptors (28). Zhang et al. showed that a young NECB patient who received goserelin and letrozole as neoadjuvant therapy achieved an excellent response (49). Neoadjuvant endocrine therapy can be used for patients with large tumors but who have a fervent desire to conserve the breast and who disagree with neoadjuvant chemotherapy. In addition, Shanks et al. presented the first patient with high-grade NECB who was resistant to platinum-based chemotherapy and hormone therapy but who obtained a remarkable response to palbociclib and the cyclin-dependent kinase (CDK) 4/6 inhibitor combined with fulvestrant (50).

HER2 positivity has been commonly related to poorly differentiated cancers of the breast. Anti-HER2 therapy can be used in sporadic cases of NECB, either in the adjuvant or metastatic setting with HER2 overexpression. Inga et al. reported a patient treated with anti-HER2 therapy in the adjuvant setting for HER-2-positive primary NECB who achieved 9-year DFS (51). Arpine treated a bone recurrent NECB patient with HER2 amplification who achieved a partial disease response after using trastuzumab (52).

Somatostatin analogues for the somatostatin receptor (SSTR) are targets for biological therapy in NETs. Somatostatin analogues show antiproliferative activity and prolonged PFS in small intestinal NETs (53). International guidelines recommend these analogues for the first-line treatment of well-differentiated G1/2 metastatic NETs. Liu et al. reported that a patient with NECB (large-cell NEC; Ki-67 proliferation index of 20%) and IDC received 177Lu-DOTATOC peptide receptor radionuclide treatment and achieved significant remission (44). Radiolabeled SSTR–targeted imaging and peptide receptor radionuclide therapy (PRRT) have demonstrated substantial benefit in managing SSTR-expressing NEN, revealing that PRRT may be a good choice for NECB (54).

In addition, NECBs may metastasize even years after treatment of the primary tumor. Therefore, long-term follow-up is recommended (55).

## FUTURE PERSPECTIVES

Although there is no specific targeted therapy strategy for NECB, several new therapeutic medicines based on specific biomarkers have been investigated in other types of breast carcinoma and in NEC of the lung and gastrointestinal pancreas, which may provide a reference for treating NECB.

TP53 is frequently mutated in most human cancers, however, targeting TP53 mutation is difficult because of its structural diversity. Identifying a compound that can target all TP53 mutations is challenging. To date, there have been no approved targeted therapies for mutant TP53. Thus, instead of directly targeting TP53, exploiting mutant TP53 synthetic lethal genes and targeting noncoding RNA networks may provide additional therapeutic benefits (56). The mutation of PIK3CA has been observed in approximately 40% of patients with HR-positive and HER2-negative advanced breast cancer, which is much higher than in NECB patients (57). Everolimus inhibits mTOR through allosteric binding to mTORC (58). Based on the results of the BOLERO-2 trial, everolimus combined with the steroidal aromatase inhibitor exemestane has become standard therapy for patients with drug-resistant HR-positive and HER2-negative terminal breast cancer resistant to prior non-steroidal aromatase inhibitor therapy (59). Alpelisib is a PI3K inhibitor and degrader, and an oral biological preparation of alpelisib has demonstrated efficacy and a safety profile combined with fulvestrant in a phase 3 SOLAR-1 study for HR-positive and HER2-negative patients with PIK3CA mutations who were previously treated with aromatase inhibitors or CDK4/6 inhibitors (60, 61). Additionally, everolimus has been approved for lung, gastrointestinal, and pancreatic NETs. Thus, targeting PIK3CA in metastatic NECB may be a promising treatment strategy based on the efficacy and safety of alpelisib and everolimus in HR-positive and HER2-negative metastatic breast cancer.

TROP-2, a transmembrane glycoprotein, was initially discovered to be expressed at high levels on the surface of trophoblastic cells, affecting the growth, invasion, and metastasis of tumors. Most TROP-2 proteins are expressed in triple-negative breast cancer (TNBC), and Vranic et al. (40) detected TROP-2 proteins in 21% of patients, indicating that TROP-2 may be a potential therapeutic target for antibody–drug conjugates. The antibody–drug conjugate, sacituzumab govitecan, which targets TROP-2, has been shown to be highly effective in heavily pretreated patients with mTNBC with good toleration (62). Mammary gland FLOR1, which encodes a leucine-rich repeat protein and is mainly expressed in TNBC, is related to worse clinical outcomes and involves cancer cell signaling and growth, suggesting that it may be a promising target for treatment strategies, such as antibody–drug conjugates (63). Mirvetuximab soravtansine is an antibody–drug conjugate that is currently being assessed in multiple clinical trials (63, 64). Although TROP-2 and FLOR1 are mainly expressed in TNBC, the discovery of TROP-2 and FLOR1 in NECB suggests that neuroendocrine carcinoma and TNBC may share some elements of molecular pathogenesis, which may aid in the development of new targeted therapy drugs for NECB. As in the era of precision medicine, it is possible to achieve the same treatment of different diseases possessing the same gene mutation or protein expression, but further clinical trials are necessary.

FGFR signaling is often deregulated in various cancers, including breast cancer and even in some cases of NECB (35). The FGFR pathway plays an essential role in tumor growth and survival, providing a promising therapeutic option for developing FGFR inhibitors. The favorable clinical benefits observed in tumors have contributed to the approval of FGFR inhibitors, including pemigatinib and infigratinib, which have been approved for patients with FGFR2 fusion/rearrangement-positive cholangiocarcinoma (65), as well as erdafitinib, which

has been approved for patients with FGFR-aberrant urothelial carcinoma (66). Thus, NECB patients with FGFR aberrations may benefit clinically from FGFR inhibitors.

Additionally, the activating mutation of KDR (VEGFR2) in some patients with NECB may provide the theoretical basis for the investigation of antiangiogenic agents in this disease. Pazopanib, an oral multitargeted tyrosine kinase inhibitor, acts through VEGFR types 1–3. A systematic review has elucidated the efficacy and safety of pazopanib in patients with locally advanced and metastatic NEN, indicating that pazopanib may be an option for NECB patients (67). Immunotherapy using checkpoint inhibitors that block PD-1/PD-L1 has emerged as a highly effective therapy in numerous patients across a range of malignancies. However, studies evaluating all currently approved biomarkers in response to PD-1/PD-L1 inhibitors have been demonstrated to be negative, indicating that NECB patients may not benefit from immunotherapy. However, PD-1/PD-L1 inhibitors have shown effectiveness on high-grade NENs from other sites with high PD-L1 expression or a high number of tumor-infiltrating lymphocytes (68).

## CONCLUSION

NECB is a rare neoplasm, and its biological behavior, clinical features, treatment, and prognosis are not yet fully understood. Although some NECB patients can benefit from conventional cytotoxic chemotherapy, others are resistant to chemotherapy. Improvements in understanding the molecular characteristics of NECB have led to the development of molecular targeted therapy for this group of diseases. In the era of precision medicine, priority should be given to identifying therapeutic targets, highlighting the role of molecular-driven studies on neuroendocrine malignancies, and modulating these targets with specific inhibitors, thus producing great clinical benefits.

## AUTHOR CONTRIBUTIONS

HS and SD reviewed the literature and drafted the article. JX and JY conceived the review and drew the tables. LL provided the pathological figures of breast primary neuroendocrine tumor. TS revised the manuscript. All authors read and approved the final manuscript.

## FUNDING

This study was partly funded by Liaoning Province Key Laboratory Project of Breast Cancer Research (2016-26-1, TS), Shenyang Breast Cancer Clinical Medical Research Center (2020-48-3-1, TS), Medical-Engineering Cross Research Fund between Liaoning Cancer Hospital and Dalian University of Technology (LD202022, TS), "Metabolic Abnormality and Tumor" Research Project (ZP202017, TS), Beijing Medical Award Foundation (YXJL-2020-0941-0752, TS), and Wu Jieping Medical Foundation (320.6750.2020-12-21,320.6750.2020-6-30,320.6750.18541, TS).

## REFERENCES

1. Hörsch D, Schmid KW, Anlauf M, Darwiche K, Denecke T, Baum RP, et al. Neuroendocrine Tumors of the Bronchopulmonary System (Typical and Atypical Carcinoid Tumors): Current Strategies in Diagnosis and Treatment. Conclusions of an Expert Meeting February 2011 in Weimar, Germany. *Oncol Res Treat* (2014) 37:266–76. doi: 10.1159/000362430
2. van der Zwan JM, Trama A, Otter R, Larrañaga N, Tavilla A, Marcos-Gragera R, et al. Rare Neuroendocrine Tumours: Results of the Surveillance of Rare Cancers in Europe Project. *Eur J Cancer (Oxford Engl 1990)* (2013) 49:2565–78. doi: 10.1016/j.ejca.2013.02.029
3. Dowd K, Rotenberry C, Russell D, Wachtel M, de Riese W. Rare Occurrence of a Poorly Differentiated Neuroendocrine Tumor of the Bladder. *Case Rep Med* (2017) 2017:4812453. doi: 10.1155/2017/4812453
4. van der Laan TP, Plaat BEC, van der Laan BFAM, Halmos GB. Clinical Recommendations on the Treatment of Neuroendocrine Carcinoma of the Larynx: A Meta-Analysis of 436 Reported Cases. *Head Neck* (2015) 37:707–15. doi: 10.1002/hed.23666
5. Bussolati G, Badve S. Carcinomas with neuroendocrine features. *In: SR Lakhani, IO Ellis, SJ Schnitt, PH Tan, MJ van der Vijver, editors. WHO Classification of Tumours of the Breast, vol. 4.* Lyon, France: IARC Press (2012). p. 62–3.
6. Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, et al. WHO Classification of Tumours of the Breast. *5th Edition. Histopathology* Lyon, France: IARC (2019).
7. Li Y, Du F, Zhu W, Xu B. Neuroendocrine Carcinoma of the Breast: A Review of 126 Cases in China. *Chin J Cancer* (2017) 36:45. doi: 10.1186/s40880-017-0211-x
8. Feyrter F, Hartmann G. On The Carcinoid Growth Form of the Carcinoma Mammae, Especially the Carcinoma Solidum (Gelatinosum) Mammae. *Frankfurter Z fur Pathologie* (1963) 73:24–39.
9. Cubilla AL, Woodruff JM. Primary Carcinoid Tumor of the Breast: A Report of Eight Patients. *Am J Surg Pathol* (1977) 1:283–92. doi: 10.1097/00000478-197712000-00001
10. Bussolati G, Gugliotta P, Sapino A, Eusebi V, Lloyd RV. Chromogranin-Reactive Endocrine Cells in Argyrophilic Carcinomas ("Carcinoids") and Normal Tissue of the Breast. *Am J Pathol* (1985) 120:186–92.
11. Sapino A, Righi L, Cassoni P, Papotti M, Pietribiasi F, Bussolati G. Expression of the Neuroendocrine Phenotype in Carcinomas of the Breast. *Semin Diagn Pathol* (2000) 17:127–37.
12. Wang J, Wei B, Albarracin C, Hu J, Abraham S, Wu Y. Invasive Neuroendocrine Carcinoma of the Breast: A Population-Based Study From the Surveillance, Epidemiology and End Results (SEER) Database. *BMC Cancer* (2014) 14:147. doi: 10.1186/1471-2407-14-147
13. Makretsov N, Gilks CB, Coldman AJ, Hayes M, Huntsman D. Tissue Microarray Analysis of Neuroendocrine Differentiation and Its Prognostic Significance in Breast Cancer. *Hum Pathol* (2003) 34:1001–8. doi: 10.1053/S0046-8177(03)00411-8
14. Lai B, Tsang J, Poon I, Shao Y, Chan S, Tam F, et al. The Clinical Significance of Neuroendocrine Features in Invasive Breast Carcinomas. *Oncologist* (2020) 25:e1318–29. doi: 10.1634/theoncologist.2020-0081
15. Park Y, Wu Y, Wei W, Yang W. Primary Neuroendocrine Carcinoma of the Breast: Clinical, Imaging, and Histologic Features. *AJR Am J roentgenology* (2014) 203:W221–230. doi: 10.2214/ajr.13.10749
16. Wei B, Ding T, Xing Y, Wei W, Tian Z, Tang F, et al. Invasive Neuroendocrine Carcinoma of the Breast: A Distinctive Subtype of Aggressive Mammary Carcinoma. *Cancer* (2010) 116:4463–73. doi: 10.1002/cncr.25352
17. Tchaou M, Darré T, Folligan K, Sabi A, Sonhaye L, Boumé A, et al. Primary Neuroendocrine Breast Carcinoma in a 13-Year-Old Girl: Ultrasonography and Pathology Findings. *Case Rep Radiol* (2017) 2017:7915806. doi: 10.1155/2017/7915806

18. Lavigne M, Menet E, Tille J, Lae M, Fuhrmann L, Bonneau C, et al. Comprehensive Clinical and Molecular Analyses of Neuroendocrine Carcinomas of the Breast. *Modern Pathol* (2018) 31:68–82. doi: 10.1038/modpathol.2017.107
19. Adams RW, Dyson P, Barthelmes L. Neuroendocrine Breast Tumours: Breast Cancer or Neuroendocrine Cancer Presenting in the Breast? *Breast (Edinburgh Scotland)* (2014) 23:120–7. doi: 10.1016/j.breast.2013.11.005
20. Santos-Juanes J, Fernández-Vega I, Coto-Segura P, Vivanco-Allende B, García-Pravia C. Cutaneous Spread of Primary Neuroendocrine Breast Carcinoma With Apocrine Differentiation. *J Eur Acad Dermatol Venereology JEADV* (2015) 29:1440–1. doi: 10.1111/jdv.12486
21. Vidulich K, Donley S, Duvic M. Multinodular Cutaneous Spread in Neuroendocrine Tumor of the Breast : An Unusual Presentation. *Am J Clin Dermatol* (2007) 8:379–83. doi: 10.2165/00128071-200708060-00008
22. Yang L, Roy M, Lin H, Shen Y, Albarracin C, Huo L, et al. Validation of Prognostic Significance of the Proposed Uniform Classification Framework in Neuroendocrine Neoplasms of the Breast. *Breast Cancer Res Treat* (2021) 186:403–15. doi: 10.1007/s10549-021-06099-6
23. Kawasaki T, Bussolati G, Marchiò C, Castellano I, Daniele L, Molinaro L, et al. Well-Differentiated Neuroendocrine Tumour of the Breast Showing Peculiar Endovascular Spread. *Histopathology* (2014) 64:597–600. doi: 10.1111/his.12276
24. Wu J, Yang Q, Wu Y, Wang D, Liu X, Cui C, et al. Solid Neuroendocrine Breast Carcinoma: Mammographic and Sonographic Features in Thirteen Cases. *Chin J Cancer* (2012) 31:549–56. doi: 10.5732/cjc.011.10370
25. Zandee WT, de Herder WW. The Evolution of Neuroendocrine Tumor Treatment Reflected by ENETS Guidelines. *Neuroendocrinology* (2018) 106:357–65. doi: 10.1159/000486096
26. Sundin A, Arnold R, Baudin E, Cwikla JB, Eriksson B, Fanti S, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Radiological, Nuclear Medicine & Hybrid Imaging. *Neuroendocrinology* (2017) 105:212–44. doi: 10.1159/000471879
27. Albright E, Keeney M, Bashir A, Weigel R. Poorly Differentiated Neuroendocrine Carcinoma of the Breast With Merkel Cell Features. *Breast J* (2018) 24:644–7. doi: 10.1111/tbj.12969
28. Shin S, DeLellis R, Ying L, Rosen P. Small Cell Carcinoma of the Breast: A Clinicopathologic and Immunohistochemical Study of Nine Patients. *Am J Surg Pathol* (2000) 24:1231–8. doi: 10.1097/00000478-200009000-00006
29. Mohanty S, Kim S, DeLair D, Bose S, Laury A, Chopra S, et al. Comparison of Metastatic Neuroendocrine Neoplasms to the Breast and Primary Invasive Mammary Carcinomas With Neuroendocrine Differentiation. *Modern Pathol* (2016) 29:788–98. doi: 10.1038/modpathol.2016.69
30. Nesland JM, Lunde S, Holm R, Johannessen JV. Electron Microscopy and Immunostaining of the Normal Breast and Its Benign Lesions. A Search for Neuroendocrine Cells. *Histol histopathology* (1987) 2:73–7.
31. Kawasaki T, Mochizuki K, Yamauchi H, Inoue S, Kondo T, Oishi N, et al. Neuroendocrine Cells Associated With Neuroendocrine Carcinoma of the Breast: Nature and Significance. *J Clin Pathol* (2012) 65:699–703. doi: 10.1136/jclinpath-2012-200765
32. Tang F, Wei B, Tian Z, Gilcrease MZ, Huo L, Albarracin CT, et al. Invasive Mammary Carcinoma With Neuroendocrine Differentiation: Histological Features and Diagnostic Challenges. *Histopathology* (2011) 59:106–15. doi: 10.1111/j.1365-2559.2011.03880.x
33. Bogina G, Munari E, Brunelli M, Bortesi L, Marconi M, Sommaggio M, et al. Neuroendocrine Differentiation in Breast Carcinoma: Clinicopathological Features and Outcome. *Histopathology* (2016) 68:422–32. doi: 10.1111/his.12766
34. Juhlin CC, Zedenius J, Höög A. Clinical Routine Application of the Second-Generation Neuroendocrine Markers ISL1, INSM1, and Secretagogin in Neuroendocrine Neoplasia: Staining Outcomes and Potential Clues for Determining Tumor Origin. *Endocrine Pathol* (2020) 31:401–10. doi: 10.1007/s12022-020-09645-y
35. Ang D, Ballard M, Beadling C, Warrick A, Schilling A, O'Gara R, et al. Novel Mutations in Neuroendocrine Carcinoma of the Breast: Possible Therapeutic Targets. *Appl Immunohistochemistry Mol Morphology AIMM* (2015) 23:97–103. doi: 10.1097/PDM.0b013e3182a40fd1
36. Perry K, Reynolds C, Rosen D, Edgerton M, T Albarracin C, Gilcrease M, et al. Metastatic Neuroendocrine Tumour in the Breast: A Potential Mimic of *In-Situ* and Invasive Mammary Carcinoma. *Histopathology* (2011) 59:619–30. doi: 10.1111/j.1365-2559.2011.03940.x
37. Miettinen M, McCue P, Sarlomo-Rikala M, Rys J, Czapiewski P, Wazny K, et al. GATA3: A Multispecific But Potentially Useful Marker in Surgical Pathology: A Systematic Analysis of 2500 Epithelial and Nonepithelial Tumors. *Am J Surg Pathol* (2014) 38:13–22. doi: 10.1097/PAS.0b013e3182a0218f
38. So J, Epstein J. GATA3 Expression in Paragangliomas: A Pitfall Potentially Leading to Misdiagnosis of Urothelial Carcinoma. *Modern Pathol* (2013) 26:1365–70. doi: 10.1038/modpathol.2013.76
39. Marchiò C, Geyer F, Ng C, Piscuoglio S, De Filippo M, Cupo M, et al. The Genetic Landscape of Breast Carcinomas With Neuroendocrine Differentiation. *J Pathol* (2017) 241:405–19. doi: 10.1002/path.4837
40. Vranic S, Palazzo J, Sanati S, Florento E, Contreras E, Xiu J, et al. Potential Novel Therapy Targets in Neuroendocrine Carcinomas of the Breast. *Clin Breast Cancer* (2019) 19:131–6. doi: 10.1016/j.clbc.2018.09.001
41. Vijayvergia N, Boland PM, Handorf E, Gustafson KS, Gong Y, Cooper HS, et al. Molecular Profiling of Neuroendocrine Malignancies to Identify Prognostic and Therapeutic Markers: A Fox Chase Cancer Center Pilot Study. *Br J Cancer* (2016) 115:564–70. doi: 10.1038/bjc.2016.229
42. Rovera F, Masciocchi P, Coglitore A, La Rosa S, Dionigi G, Marelli M, et al. Neuroendocrine Carcinomas of the Breast. *Int J Surg (London England)* (2008), 6(1):S113–115. doi: 10.1016/j.ijsu.2008.12.007
43. Kwon SY, Bae YK, Gu MJ, Choi JE, Kang SH, Lee SJ, et al. Neuroendocrine Differentiation Correlates With Hormone Receptor Expression and Decreased Survival in Patients With Invasive Breast Carcinoma. *Histopathology* (2014) 64:647–59. doi: 10.1111/his.12306
44. Liu Q, Zhang J, Kulkarni HR, Baum RP. 177Lu-DOTATOC Peptide Receptor Radionuclide Therapy in a Patient With Neuroendocrine Breast Carcinoma and Breast Invasive Ductal Carcinoma. *Clin Nucl Med* (2020) 45:e232–5. doi: 10.1097/RLU.0000000000003005
45. Bongiovanni A, Liverani C, Foca F, Fausti V, Di Menna G, Mercatali L, et al. Temozolomide Alone or Combined With Capecitabine for the Treatment of Metastatic Neuroendocrine Neoplasia: A "Real-World" Data Analysis. *Neuroendocrinology* (2021) 111:895–906. doi: 10.1159/000513218
46. Atchison L, Hardy T, Mancl T, Quaranta B, Madan A. Locally Advanced Primary Small Cell Carcinoma of the Breast: A Case Report and Review of Current Evidence. *Case Rep Oncol* (2021) 14:761–6. doi: 10.1159/000515505
47. Wei X, Chen C, Xi D, Bai J, Huang W, Rong L, et al. A Case of Primary Neuroendocrine Breast Carcinoma That Responded to Neo-Adjuvant Chemotherapy. *Front Med* (2015) 9:112–6. doi: 10.1007/s11684-014-0345-z
48. Sanguinetti A, Santoprete S, Lucchini R, Triola R, Loreti F, Avenia N. A Rare Breast Tumor: Solid Neuroendocrine Carcinoma. *Annali italiani di chirurgia* (2012) 84:1–5.
49. Zhang Y, Liu C, Zheng C, Ren Q, Wang Q, Gao X, et al. Efficacy of Neoadjuvant Endocrine Therapy in Patients With Poorly Differentiated Neuroendocrine Carcinoma of the Breast: A Case Report. *Medicine* (2020) 99:e22652. doi: 10.1097/md.0000000000022652
50. Shanks A, Choi J, Karur V. Dramatic Response to Cyclin D-Dependent Kinase 4/6 Inhibitor in Refractory Poorly Differentiated Neuroendocrine Carcinoma of the Breast. *Proc (Baylor University Med Center)* (2018) 31:352–4. doi: 10.1080/08998280.2018.1463041
51. Marijanović I, Kraljević M, Buhovac T, Karan Križanac D. Rare Human Epidermal Growth Factor Receptor 2 (HER-2)-Positive Neuroendocrine Carcinoma of the Breast: A Case Report With 9-Year Follow-Up. *Am J Case Rep* (2020) 21:e925895. doi: 10.12659/ajcr.925895
52. Gevorgyan A, Bregni G, Galli G, Zanardi E, de Braud F, Di Cosimo S. HER2-Positive Neuroendocrine Breast Cancer: Case Report and Review of Literature. *Breast Care (Basel Switzerland)* (2016) 11:424–6. doi: 10.1159/000453572
53. Bongiovanni A, Recine F, Foca F, Fausti V, Riva N, Fabbri G, et al. Metastatic Neuroendocrine Neoplasia Treatments in Patients Over 70 Years of Age. *Endocrine connections* (2018) 7:1535–41. doi: 10.1530/EC-18-0478
54. O'Dorisio TM, Harris AG, O'Dorisio MS. Evolution of Neuroendocrine Tumor Therapy. *Surg Oncol Clinics North America* (2020) 29:145–63. doi: 10.1016/j.soc.2019.11.002
55. Valente I, Tringali G, Martella E, Pallavera L, D'Aloia C. Primary Neuroendocrine Carcinoma of the Breast: A Case Report of Liver and Lymph Node Metastases After Eight Years From Diagnosis. *Breast J* (2020) 26:505–7. doi: 10.1111/tbj.13535

56. Hu J, Cao J, Topatana W, Juengpanich S, Li S, Zhang B, et al. Targeting Mutant P53 for Cancer Therapy: Direct and Indirect Strategies. *J Hematol Oncol* (2021) 14:157. doi: 10.1186/s13045-021-01169-0
57. The Cancer Genome Atlas Network. Comprehensive Molecular Portraits of Human Breast Tumours. *Nature* (2012) 490:61–70. doi: 10.1038/nature11412
58. Efeyan A, Sabatini D. mTOR and Cancer: Many Loops in One Pathway. *Curr Opin Cell Biol* (2010) 22:169–76. doi: 10.1016/j.ceb.2009.10.007
59. Baselga J, Campone M, Piccart M, Burris H, Rugo H, Sahmoud T, et al. Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer. *New Engl J Med* (2012) 366:520–9. doi: 10.1056/NEJMoa1109653
60. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo H, et al. PIK3CAAlpelisib for -Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med* (2019) 380:1929–40. doi: 10.1056/NEJMoa1813904
61. Rugo H, Lerebours F, Ciruelos E, Drullinsky P, Ruiz-Borrego M, Neven P, et al. Alpelisib Plus Fulvestrant in PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer After a CDK4/6 Inhibitor (BYLieve): One Cohort of a Phase 2, Multicentre, Open-Label, Non-Comparative Study. *Lancet Oncol* (2021) 22:489–98. doi: 10.1016/s1470-2045(21)00034-6
62. Bardia A, Mayer I, Diamond J, Moroose R, Isakoff S, Starodub A, et al. Efficacy and Safety of Anti-Trop-2 Antibody Drug Conjugate Sacituzumab Govitecan (IMMU-132) in Heavily Pretreated Patients With Metastatic Triple-Negative Breast Cancer. *J Clin Oncol* (2017) 35:2141–8. doi: 10.1200/jco.2016.70.8297
63. Cheung A, Opzoomer J, Ilieva K, Gazinska P, Hoffmann R, Mirza H, et al. Anti-Folate Receptor Alpha-Directed Antibody Therapies Restrict the Growth of Triple-Negative Breast Cancer. *Clin Cancer Res* (2018) 24:5098–111. doi: 10.1158/1078-0432.Ccr-18-0652
64. Ab O, Whiteman KR, Bartle LM, Sun X, Singh R, Tavares D, et al. IMGN853, a Folate Receptor-α (Frα)-Targeting Antibody-Drug Conjugate, Exhibits Potent Targeted Antitumor Activity Against Frα-Expressing Tumors. *Mol Cancer Ther* (2015) 14:1605–13. doi: 10.1158/1535-7163.MCT-14-1095
65. Abou-Alfa G, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for Previously Treated, Locally Advanced or Metastatic Cholangiocarcinoma: A Multicentre, Open-Label, Phase 2 Study. *Lancet Oncol* (2020) 21:671–84. doi: 10.1016/s1470-2045(20)30109-1
66. Loriot Y, Necchi A, Park S, Garcia-Donas J, Huddart R, Burgess E, et al. Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. *N Engl J Med* (2019) 381:338–48. doi: 10.1056/NEJMoa1817323
67. Bongiovanni A, Liverani C, Recine F, Fausti V, Mercatali L, Vagheggini A, et al. Phase-II Trials of Pazopanib in Metastatic Neuroendocrine Neoplasia (mNEN): A Systematic Review and Meta-Analysis. *Front Oncol* (2020) 10:414. doi: 10.3389/fonc.2020.00414
68. Vijayvergia N, Dasari A, Deng M, Litwin S, Al-Toubah T, Alpaugh R, et al. Pembrolizumab Monotherapy in Patients With Previously Treated Metastatic High-Grade Neuroendocrine Neoplasms: Joint Analysis of Two Prospective, non-Randomised Trials. *Br J Cancer* (2020) 122:1309–14. doi: 10.1038/s41416-020-0775-0


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 30 May 2022
doi: 10.3389/fonc.2022.819756

# Associations Between Serum Reproductive Hormone Concentrations and Hormonal Receptor Status Among Postmenopausal Chinese Women With Breast Cancer: An Observational Study

*Chuner Jiang*[1,2], *Peng Wu*[2,3], *Xiangming He*[1,2], *Jianfen Ni*[1,2], *Xiaowen Ding*[1,2], *Xiaohong Xu*[2,4], *Fangzheng Wang*[2,5*] and *Dehong Zou*[1,2*]

[1] Department of Breast Tumor Surgery, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China, [2] Institute of Cancer and Basic Medicine (ICBM), Chinese Academy of Sciences, Hangzhou, China, [3] Pathology Department, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China, [4] Clinic Laboratory, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China, [5] Department of Radiation Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China

OPEN ACCESS

**Edited by:**
Julio de la Torre,
Comillas Pontifical University, Spain

**Reviewed by:**
Jelena Milovanovic,
Institute of Oncology and Radiology of Serbia, Serbia
Marko Radulovic,
Institute of Oncology and Radiology of Serbia, Serbia

***Correspondence:**
Dehong Zou
zoudh1964@126.com
Fangzheng Wang
wangfz@zjcc.org.cn

**Specialty section:**
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

**Received:** 22 November 2021
**Accepted:** 25 April 2022
**Published:** 30 May 2022

**Citation:**
Jiang C, Wu P, He X, Ni J, Ding X, Xu X, Wang F and Zou D (2022) Associations Between Serum Reproductive Hormone Concentrations and Hormonal Receptor Status Among Postmenopausal Chinese Women With Breast Cancer: An Observational Study. Front. Oncol. 12:819756. doi: 10.3389/fonc.2022.819756

**Background and Objectives:** Reproductive hormones and receptors play crucial roles in breast cancer development and progression. The association between preoperative serum reproductive hormone levels and receptor status in postmenopausal women with breast cancer remains unclear. Therefore, this study investigated the relationship between serum reproductive hormone concentrations and patient characteristics and hormone receptor status among postmenopausal Chinese women with breast cancer.

**Materials and Methods:** The medical records of 352 postmenopausal breast cancer patients who underwent an operation between October 2007 and October 2010 at the Department of Breast Tumor Surgery of Zhejiang Cancer Hospital were retrospectively evaluated. Serum levels of reproductive hormones were measured before surgery by liquid-chromatography tandem mass spectrometry. Hormone receptor levels were measured by an immunohistochemical assay using a mouse monoclonal antibody. The associations between serum hormone concentrations and hormone receptors were investigated by analysis of covariance.

**Results:** In this patient cohort, the serum level of luteinizing hormone (LH) declined with PMP duration. The median LH concentration was significantly higher in patients within 5 years of PMP than that in patients with PMP duration exceeding 5 years (23 vs. 18.32 mIU/ml, $P$ <.0001). Significantly more patients with strong estrogen receptor (ER) or progesterone receptor (PR) expression had postmenopausal durations of less than 5 years compared to those with postmenopausal durations greater than 5 years (103 vs. 61

cases, $P = .019$; 93 vs. 46 cases, $P = .0005$). While most patients either lacked (97.1%) or co-expressed (84.3%) ER and PR, some patients expressed either ER or PR alone. ER and PR expression were negatively associated with receptor-tyrosine kinase erbB-2 (HER2) expression in postmenopausal patients with breast cancer. Meanwhile, increased ER and PR expression were associated with decreased serum levels of LH or follicle-stimulating hormone (FSH).

**Conclusion:** Decreased serum LH and FSH levels were associated with increased ER and PR expressions and decreased HER2 expression in postmenopausal patients with breast cancer.

**Keywords: breast cancer, postmenopausal, reproductive hormones, estrogen receptor, progesterone receptor, HER2 receptor**

## INTRODUCTION

Breast cancer is one of the most common cancers in women worldwide, with an annually increasing incidence (1, 2). In 2020, 276,480 new patients with breast cancer and 42,170 deaths occurred in the United States (3). However, in China, the incidence rate of breast cancer is more than twice that of the world, and the incidence of elderly patients with breast cancer is also rising (4). The increase is related to changes in reproductive patterns and the use of mammography screening. Meanwhile, the trend is also associated with physical inactivity, lifestyle changes, menopausal hormone use, and the prevalence of obesity (5).

Breast cancer is a unique disease with multiple clinical subtypes. However, its pathogenesis remains unclear (6). De Waard first proposed the presence of two pathways and age-specific incidence rate curves in breast cancer (7, 8). In one pathway, the incidence of premenopausal breast cancer peaks early in life, while the peak incidence of postmenopausal disease in the second pathway occurs later in life. The two peak ages reported in China were 45–55 and 70–74 years, respectively (9).

While the causes leading to the development of breast cancer are unknown, the associated risk factors include age and elements related to reproductive life (10). Among those risk factors, hormones such as estrogen (E) and progesterone (P) play an important role in accelerating breast cancer cell growth. Furthermore, the cumulative exposure to hormones such as E and P also increases the likelihood of breast cancer (11–13).

The serum estrogens include estrone (E1), estradiol (E2), and estriol (E3). Among these estrogens, E2 affects cell proliferation and apoptosis by interacting with the estrogen receptor (ER) in breast tissue, thus affecting the development and progression of breast cancer (14). Furthermore, E2 levels were positively correlated with the risk of postmenopausal breast cancer (15–17).

Breast cancer cells express the ER or progesterone receptor (PR), and about two-thirds of breast cancers are ER-positive and/or PR-positive (18). Breast cancer cells expressing ER or PR require E or P to grow. In addition to ER and PR, receptor tyrosine-protein kinase erbB-2 (HER2) plays a crucial role in breast cancer progression (19). Cancer cells with increased HER2 expression tend to grow and spread more aggressively compared to cancer cells lacking HER2 expression (20). Clinically, the positivity status of ER, PR, or HER2 alone or in combination is critically involved in the selection of therapeutic approaches and determines patient outcomes in breast cancer (21, 22).

Like other types of cancer, the incidence of breast cancer increases with age. Approximately two-thirds of invasive breast cancers occur in women aged 55 years or older; thus, most patients with breast cancer are postmenopausal. However, whether postmenopausal duration affects hormone levels and hormone receptor expression remains unknown. This study measured serum levels of reproductive hormones, namely, luteinizing hormone (LH), E2, P, testosterone (T), follicle-stimulating hormone (FSH), and prolactin (PRL) in postmenopausal patients with breast cancer. The expression levels of ER, PR, HER2, and p53 were also determined. Furthermore, the relationships between these receptors and hormones were evaluated.

## MATERIALS AND METHODS

This study included 352 postmenopausal patients diagnosed with breast cancer. The diagnosis was made on the basis of pathological findings from thick-needle biopsy specimens of breast tissues and included invasive ductal carcinoma *in situ* (DCIS). We retrospectively extracted and analyzed data from the patient database of this cohort from October 2007 to October 2010. These data were gathered prior to undergoing chemotherapy, radiotherapy, or hormone therapy. No patients had chronic hepatitis or nephritis, and all had normal liver and renal functions.

This study was reviewed and approved by the Medical Ethics Committee of Zhejiang Cancer Hospital of China. The patients provided their written informed consent.

### Serum Hormonal Levels

The serum concentrations of six hormones (LH, E2, T, P, FSH, and PRL) were assayed before the patients underwent surgery.

**Abbreviations:** PMP, postmenopausal; LH, luteinizing hormone; ER, estrogen receptor; PR, progesterone receptor; HER2, receptor-tyrosine kinase erbB-2; FSH, follicle-stimulating hormone; DCIS, ductal carcinoma *in situ*; E, estrogen; E2, estradiol; P, progesterone; T, testosterone; PRL, prolactin; FISH, fluorescence *in situ* hybridization.

The concentrations were measured by chemiluminescence immunoassay (CLIA) on a UniCel DxI 800 system (Beckman Coulter, Brea, CA, USA) following the instructions of the manufacturer for routine laboratory tests. The laboratory standard values for these hormones were 7.7–58.5 mIU/ml for LH, 10–40 pg/ml for E2, 0–.78 pg/ml for P, 0–0.75 pg/ml for T, 25.8–113.59 pg/ml for FSH, and 0–19.64 pg/ml for PRL.

## Determination of Hormone Receptor Status

Less than 30 min after surgery, the tumor specimens were fixed with 4% neutral formalin and embedded in paraffin blocks. The blocks were subsequently sliced into 4-μm sections. Immunohistochemistry was performed using a Universal DAB Detection kit (Ventana Medical Systems, Tucson, AZ, USA) following the instructions of the manufacturer. Anti-ER (clone No. SPl) and anti-PR (clone No. PgR636) monoclonal antibodies were purchased from Dako, Inc. (Carpinteria, CA, USA), and an anti-HER2 monoclonal antibody (clone No. 4B5) was also used. The expressions of P53 and TOPO II in the study were assessed using monoclonal anti-P53 antibody (cat.nos: ab131442) and anti-TOPO II antibody (clone KISI-DAKO, UK/DN dilution 1:50).

ER and PR staining was assessed as described in the "Immunohistochemistry guide for the staining of estrogen and progesterone receptor in breast cancer (2015 edition in Chinese)," with a slight modification (**Figure 1**). ER or PR positivity or negativity was defined according to the percentages of nuclear-stained cells among all tumor cells in the entire section. Cases with percentages above 10% were defined as positive. If nuclear staining was absent or the percentage of nuclear-staining cells was less than 10%, the case was defined as negative. The ER and PR-positive cases were further divided into three groups based on nuclear staining intensity as weak (pale-yellow, +), intermediate (brown-yellow, ++), and strong (dark-brown, +++).

HER2 staining was assessed as described in the "Testing guide for the staining of HER2 in breast cancer (2014 edition in Chinese)." HER2 staining in each case was scored as 0, +, ++, or +++ (**Figure 1**). A (0) score indicated no or incomplete and weak membrane staining in ≤10% of cancer cells. A (+) score indicated an incomplete and weak membrane staining in > 10% of cancer cells. A (++) score indicated an incomplete and/or weak to moderate membrane staining in >10% of cancer cells or strong and complete membrane staining in ≤10% of cancer cells. A (+++) score was defined as strong and complete membrane staining in >10% of cancer cells. HER2 was considered negative or positive for scores of (0)/(+) and (+++), respectively. A (++) HER2 score was defined as uncertain, and further tests such as fluorescence *in situ* hybridization (FISH) or genotyping were required to confirm positivity.

The scoring and intensity of P53 were evaluated using light microscopy (100*) according to the methods of Papamistou et al. (23). So, we characterized P53 expression as negative, weak, and strong.

The TOPO II protein expression levels were assessed by measuring the corresponding staining intensity levels provided by digital image analysis. Using normal epithelia as the control group, we characterized TOPO II expression as negative, weak, and strong.

## Statistical Analysis

In the analysis section, IBM statistics could be cited as IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.

# RESULTS

The characteristics of 352 postmenopausal patients with breast cancer who were enrolled in this study are summarized in

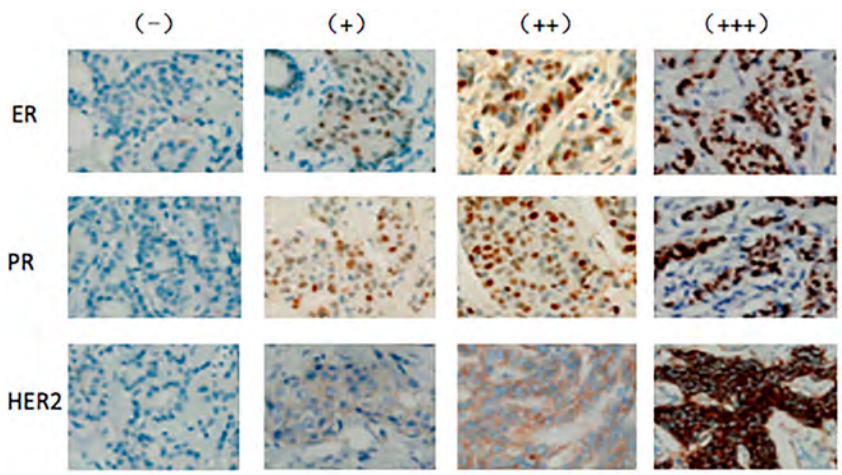



**FIGURE 1** | Expression of ER, PR, and HER2 in PMP patients with breast cancer Expression levels of ER, PR, and HER2 were determined by immunohistochemistry and assessed by staining intensity from no expression (–) to weak (+), intermediate (++), and strong (+++) staining.

**Table 1**. The median age of this cohort was 57 years, with most (58.81%) patients aged 50–59 years; 1.99 and 11.36% were aged below 50 or above 70 years, respectively. Pathologically, 278 of the 352 (78.98%) patients had invasive ductal carcinoma, a dominant type of breast cancer. In this cohort, 58.24 and 48.01% of patients expressed ER and PR, respectively. Most patients (76.7%) were HER2-positive.

We first measured the serum levels of six hormones (LH, E2, T, P, FSH, and PRL) in postmenopausal patients with breast cancer by CLIA. We arbitrarily divided the patient cohort into four groups based on postmenopausal duration (1–5, 6–10, 11–20, and more than 21 years). The median values and ranges of each hormone are listed in **Table 2**. Serum levels of E2 and P were less than 10 pg/ml and 0.1 ng/ml, respectively, with undetectable values in 66.9% (228 of 341) and 22.6% (77 of 341) of the patients, respectively.

Among the six hormones, the serum level of LH declined with postmenopausal duration in this patient cohort. The median LH value was significantly higher in patients with a postmenopausal duration of 5 years or less (23 mIU/ml) than in patients with a postmenopausal duration exceeding 5 years (18.32 mIU/ml, $P$ <.0001). The difference between the postmenopausal duration of 1–5 years and the postmenopausal duration of 11–20 or ≥21 years was also significant. However, a significant difference in the serum levels of other hormones in patients with different postmenopausal durations was not observed.

We subsequently determined hormone receptor (ER, PR, and HER2) expression by immunohistochemistry. As shown in **Figure 1**, the expression levels of these hormone receptors varied from negative to weak positive (+) and strong positive (++ and +++ combined). To simplify the analysis, we arbitrarily divided the patient cohort into two groups based on postmenopausal duration (1–5 and ≥6 years). The numbers of patients expressing variable levels of hormone receptors are listed in **Table 3**. The number of women with strong ER and PR expression was significantly higher in patients with a postmenopausal duration exceeding 5 years (103 and 93 cases, respectively) than in patients with a postmenopausal duration of up to 5 years (61 and 46 cases, $P$ = .019 and $P$ = .0005, respectively). No differences in HER2 expression levels in breast cancer patients according to postmenopausal duration were observed.

In addition to hormone receptors, we measured the expression of tumor proteins p53 and type II topoisomerase in this patient cohort and found no differences in the expression among postmenopausal patients with breast cancer.

We subsequently analyzed the association between hormones and hormone receptors in postmenopausal patients with breast cancer. As shown in **Table 4**, patients with strong tumor ER or PR expression (++ and +++ combined) had significantly reduced serum LH levels (18.6 and 19.1 mIU/ml, respectively) compared to those in patients without tumor ER or PR expression (21.7 and 21 mIU/ml, $P$ = .001 and.008, respectively). As well, the levels of FSH (52.415 and 51.39 pg/ml, respectively) in patients with strong tumor ER or PR expression were lower than those in patients without tumor ER or PR expression (55.6 and 53.9 pg/ml, P = 0.03

**TABLE 1** | Patients' characteristics.

| Characteristics | Variance | N | % |
|---|---|---|---|
| Age (years) | 40–49 | 7 | 1.99 |
| | 50–59 | 207 | 58.81 |
| | 60–69 | 98 | 27.84 |
| | 70 above | 40 | 11.36 |
| Pathology | Invasive ductal | 278 | 78.98 |
| | Others | 74 | 21.02 |
| ER expression | +++ | 124 | 35.23 |
| | ++ | 40 | 11.36 |
| | + | 30 | 8.52 |
| | – | 147 | 41.76 |
| PR expression | +++ | 63 | 17.90 |
| | ++ | 54 | 15.34 |
| | + | 41 | 11.65 |
| | – | 183 | 51.99 |
| HER2 expression | +++ | 77 | 21.88 |
| | ++ | 100 | 28.41 |
| | + | 72 | 20.45 |
| | – | 82 | 23.30 |

*ER, estrogen receptor; PR, progesterone receptor; HER2, receptor-tyrosine kinase erbB-2.*

**TABLE 2** | Association of PMP years with hormones in breast cancer patients.

| PMP years | | Hormones | | | | | |
|---|---|---|---|---|---|---|---|
| | | LH | E2 | P | T | FSH | PRL |
| 1–5 | N | 154 | 55 | 123 | 152 | 154 | 153 |
| | Median | 23 | 13.5 | 0.1 | 0.44 | 54.98 | 13.85 |
| | Range | 3.56–57.8 | 11–120 | 0.1–1.3 | 0.08–4.7 | 3.2–138 | 3.52–89.6 |
| 6–10 | N | 77 | 26 | 62 | 77 | 77 | 77 |
| | Median | 19.48 | 12 | 0.1 | 0.42 | 54.7 | 12.23 |
| | Range | 6.13–50.2 | 11–22 | 0.1–0.6 | 0.13–1.2 | 0.86–150 | 4.51–114 |
| 11–20 | N | 81 | 26 | 59 | 81 | 81 | 81 |
| | Median | 17.36 | 13 | 0.1 | 0.46 | 50.97 | 11.84 |
| | Range | 1.16–46.1 | 11–36 | 0.1–0.7 | 0.08–1.4 | 5.6–150 | 0.03–161 |
| ≥21 | N | 29 | 6 | 20 | 29 | 29 | 29 |
| | Median | 16.87 | 10.5 | 0.1 | 0.39 | 54.38 | 12.67 |
| | Range | 8.01–32.4 | 11–17 | 0.1–0.8 | 0.08–1.15 | 27.92–150 | 6.3–34.32 |
| P | | 0.0001* | <0.05 | <0.05 | <0.05 | <0.05 | <0.05 |

*PMP, postmenopausal; LH, luteinizing hormone; E2, estradiol; P, progesterone; T, testosterone; FSH, follicle-stimulating hormone; PRL, prolactin.*
**Comparison between group of PMP 1–5 and group of PMP 6 above.*

**TABLE 3 |** Association between PMP and hormone receptors in breast cancer patients.

| Hormones receptors | | PMP (years) | | P |
|---|---|---|---|---|
| | | 1–5 (n) | 6 above (n) | |
| ER expression | Negative | 74 | 73 | 0.019* |
| | Weak positive | 19 | 11 | |
| | Strong positive | 61 | 103 | |
| PR expression | Negative | 89 | 94 | 0.005* |
| | Weak positive | 19 | 32 | |
| | Strong positive | 46 | 93 | |
| HER2 expression | Negative | 32 | 50 | 0.091 |
| | Weak positive | 30 | 42 | |
| | Strong positive | 89 | 88 | |
| P53 expression | Negative | 56 | 78 | 0.542 |
| | Weak positive | 37 | 42 | |
| | Strong positive | 44 | 52 | |
| TOPO II expression | Negative | 16 | 32 | 0.284 |
| | Weak positive | 47 | 51 | |
| | Strong positive | 6 | 6 | |

*PMP, postmenopausal; ER, estrogen receptor; PR, progesterone receptor; HER2, receptor-tyrosine kinase erbB-2; TOPO II, topoisomerase II.*
**Comparison between group of negative and group of strong positive.*

and P = 0.031, respectively). In contrast, patients with strong tumor HER2 expression had significantly elevated serum LH levels (22.1 mIU/ml) compared to those in patients without tumor HER2 expression (18.3 mIU/ml, *P* = .011). No associations between p53 expression and serum levels of any hormone were observed in postmenopausal patients with breast cancer.

A chi-square analysis to evaluate the association between these three hormone receptors in postmenopausal patients with breast cancer showed a strong positive association between ER and PR expression in this patient cohort. As shown in **Table 5**, the number of patients who were double-negative or double-positive for ER and PR was significantly higher than those of patients with single-negative or -positive ER or PR status. Among 173 patients without an ER expression, 168 (97.1%) cases also lacked PR expression. However, 84.3% (54 of 64) of the patients with a strong PR expression (+++) also had a strong ER expression.

In contrast, we observed a negative association between the expression of HER2 and ER or PR in postmenopausal patients with breast cancer. Patients without ER or PR expression tended to have a strong HER2 expression and vice versa. Among the 146 and 182 patients without ER and PR expression, 90 (61.6%) and 112 (61.5%) cases had strong ER expression (++/+++), respectively. In contrast, only 13 (16.5) and 4 (5.1%) of 79 patients with strong HER2 expression (+++) had strong ER or PR expression, respectively.

## DISCUSSION

Circulating reproductive hormones play an important role in breast cancer development and progression. Long-term exposure to high amounts of E in the blood increases the risk of breast cancer (24, 25). Binding to receptors, hormones accelerate breast cell proliferation. A previous study showed that higher circulating E1 and E2 increased the incidence of breast cancer (26). Furthermore, the levels of E2 in postmenopausal Chinese

**TABLE 5 |** Association between any two hormones receptors.

| Hormones receptors | | ER | | | | | HER2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | – | + | + + | ++ + | P | – | + | + + | ++ + | p |
| PR | – | 168 | 13 | 11 | 16 | 0.001* | 34 | 36 | 53 | 59 | 0.001* |
| | + | 5 | 10 | 9 | 20 | | 12 | 11 | 11 | 8 | |
| | ++ | 0 | 5 | 16 | 36 | 0.001# | 16 | 11 | 21 | 7 | 0.001# |
| | +++ | 0 | 3 | 7 | 54 | | 24 | 16 | 7 | 4 | |
| HER2 | – | 28 | 11 | 7 | 40 | 0.001* | | | | | |
| | + | 28 | 6 | 8 | 33 | | | | | | |
| | ++ | 38 | 7 | 20 | 39 | 0.022# | | | | | |
| | +++ | 52 | 7 | 7 | 13 | | | | | | |

**Comparison between (–) group and (+++) group, #Comparison between (–) group and (++/+++) combined group.*

**TABLE 4 |** Association between hormones and hormone receptors.

| Receptors | | Hormones | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | LH | p | E2 | p | P | p | T | p | FSH | p | PRL | p |
| ER expression | Negative | 21.7 | 0.001 | 13 | 0.99 | 0.1 | 0.38 | 0.41 | 0.06 | 55.6 | 0.03 | 13.42 | 0.37 |
| | Weak postive | 21 | | 15 | | 0.2 | | 0.42 | | 54.84 | | 14.17 | |
| | Strong positive | 18.63 | | 12 | | 0.1 | | 0.44 | | 52.415 | | 12.6 | |
| PR expression | Negative | 20.99 | 0.008 | 10 | 0.52 | 0.1 | 0.72 | 0.405 | 0.015 | 53.9 | 0.031 | 13.54 | 0.65 |
| | Weak postive | 20.03 | | 10 | | 0.2 | | 0.37 | | 13.0 | | 14.71 | |
| | Strong positive | 19.05 | | 10 | | 0.1 | | 0.49 | | 51.39 | | 11.55 | |
| HER 2 expression | Negative | 18.33 | 0.011 | 14 | 0.011 | 0.1 | 0.99 | 0.44 | 0.93 | 51.25 | 0.07 | 11.62 | 0.18 |
| | Weak postive | 17.59 | | 13 | | 0.1 | | 0.37 | | 49.53 | | 13.32 | |
| | Strong positive | 22.05 | | 12 | | 0.1 | | 0.43 | | 58.44 | | 13.525 | |
| P53 expression | Negative | 20.08 | 0.20 | 13 | 0.87 | 0.1 | 0.80 | 0.425 | 0.58 | 54.34 | 0.19 | 13.42 | 0.79 |
| | Weak postive | 18.73 | | 12 | | 0.1 | | 0.49 | | 51.86 | | 12.23 | |
| | Strong positive | 20.79 | | 12 | | 0.1 | | 0.40 | | 53.82 | | 12.32 | |

*ER, estrogen receptor; PR, progesterone receptor; HER2, receptor-tyrosine kinase erbB-2; LH, luteinizing hormone; E2, estradiol; P, progesterone; T, testosterone; FSH, follicle-stimulating hormone; PRL, prolactin.*
*p Comparison between group of negative and group of strong positive.*

patients with breast cancer were higher than those of healthy subjects (27). This study focused on postmenopausal patients to explore the association between hormones and hormone receptors since a menstrual cycle-mediated variation in serum hormone levels is minimized in postmenopausal patients. To our knowledge, this is the first study to comprehensively measure the levels of reproductive hormones and receptors in a relatively large cohort of postmenopausal patients with breast cancer.

LH, FSH, and PRL are produced by the pituitary gland and affect the ovaries. In FSH stimulation of ovarian follicles to produce estrogen, whereas LH stimulates the corpus luteum to secrete P in premenopausal women. With ovarian atrophy, the production of E and P drops with increasing postmenopausal duration. In this study, the serum levels of LH, FSH, and PRL decreased in the years following menopause, although their levels remained stable in patients who had experienced postmenopausal more than 21 years ago. While some postmenopausal patients maintained normal E2 and T levels, a significant number of patients (66.9% for E2 and 22.6% for T) had undetectable concentrations of these hormones, suggesting a clinical indication for E therapy in this patient population.

ER and PR are the most widely studied markers in breast cancer (28), and their expression levels are used as predictive markers of response to endocrine therapy (29). This study assessed the effects of postmenopausal on ER and PR expression in breast cancer and found that ER and PR expression were significantly associated with postmenopausal duration. Considering the inhibitory effect of the hormones on ER and PR expression, the enhanced expression may be the result of a decline in E and P levels in postmenopausal patients.

ER and PR expression were significantly correlated with postmenopausal patients with breast cancer. The number of patients with double-negative or double-positive ER and PR expression was significantly higher than those with single-negative ER and PR expression. We observed patients with single-positive ER or PR expression. Nadji et al. analyzed 5,993 patients with breast cancer and found no cases that were ER-negative but PR-positive (30). In contrast, other studies have reported independent expression of ER and PR (31, 32), consistent with our findings.

It is unclear whether hormone levels correlate with ER or PR expression in breast cancer patients. In this cohort, we observed a positive correlation between serum hormone levels and ER or PR expression, consistent with previous reports of the inhibitory effect of estrogen on ER or PR expression (33). In contrast, the hormone levels were higher in HER2-positive patients than in HER2-negative patients, supporting the observed negative association between ER or PR and HER2 expression.

Some limitations of this study should be considered when interpreting these results. First, this retrospective study involved patients from a single center. Second, we evaluated only the relationship between serum reproductive hormone concentration and patient characteristics and hormone receptor status among post-menopausal Chinese women; the survival outcomes were not considered. Finally, records of patients were partly dismissed. Therefore, these results should be regarded as preliminary, and additional prospective, randomized, large-sample, multi-center phase III clinical trials must confirm our findings.

## Conclusion

The results of this study showed decreased serum hormone levels over the postmenopausal course in patients with breast cancer. The number of patients with strong ER and PR or negative HER2 expression increased in the later years compared with the early years of PMP. While most patients either lacked or co-expressed ER and PR, some patients expressed either ER or PR alone. ER and PR expression were negatively associated with HER2 expression in postmenopausal patients with breast cancer. Increased ER and PR expression was associated with decreased serum LH or FSH levels. These results indicated that postmenopausal-mediated decreases in serum LH and FSH levels were associated with increased ER and PR expression and decreased HER2 expression in patients with breast cancer. Overall, the present findings provide an improved understanding of the association between hormones and receptors in postmenopausal patients with breast cancer.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Zhejiang Cancer Hospital of China. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

FW and DZ contributed to conception and design of the study. CJ, PW, XH, XD, XX, and JN organized database. CJ wrote the first draft of the manuscript. CJ, FW, and DZ wrote sections of the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

## FUNDING

The authors declare that this study received funding from the Medical and Health Science and Technology Program of Zhejiang Province (Nos. 2020KY084, 2019KY041, 2011RCA014, 2006A016, and 2005B012), the National Natural Science Foundation of Zhejiang Province of China (LY15H1800012015), and the National Natural Science Foundation of China (Nos. 81502646 and 81502647).

## REFERENCES


1. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al. Colorectal Cancer Statistics, 2017. *CA Cancer J Clin* (2017) 67:177–93. doi: 10.3322/caac.21395
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer Statistics in China, 2015. *CA Cancer J Clin* (2016) 66:115–32. doi: 10.3322/caac.21338
3. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2020. *CA Cancer J Clin* (2020) 70(1):7–30. doi: 10.3322/caac.21590
4. Fan L, Strasser-Weippl K, Li JJ, St Louis J, Finkelstein DM, Yu KD, et al. Breast Cancer in China. *Lancet Oncol* (2014) 15(7):e279–89. doi: 10.1016/S1470-2045(13)70567-9
5. DeSantis C, Ma J, Bryan I, Jemal A. Breast Cancer Statistics, 2013. *CA Cancer J Clin* (2014) 64(1):52–62. doi: 10.3322/caac.21203
6. Anderson WF, Rosenberg PS, Prat A, Perou CM, Sherman ME. How Many Etiological Subtypes of Breast Cancer: Two, Three, Four, or More? *J Natl Cancer Inst* (2014) 106:296–7. doi: 10.1016/j.breastdis.2015.10.037
7. De WF, Baanders-Vanhalewijn EA, Huizinga J. The Bimodal Age Distribution of Patients With Mammary Carcinoma; Evidence for the Existence of 2 Types of Human Breast Cancer. *Cancer* (1964) 17:141–51. doi: 10.1002/1097-0142(196402)17:2<141::AID-CNCR2820170202>3.0.CO;2-Z
8. Waard FD. Premenopausal and Postmenopausal Breast Cancer: One Disease or Two? *J Natl Cancer Inst* (1979) 63:549–52. doi: 10.1093/jnci/63.3.549
9. Fan L, Zheng Y, Yu KD, Liu GY, Wu J, Lu JS, et al. Breast Cancer in a Transitional Society Over 18 Years: Trends and Present Status in Shanghai, China. *Breast Cancer Res Treat* (2009) 117:409–16. doi: 10.1007/s10549-008-0303-z
10. Anderson KN, Schwab RB, Martinez ME. Reproductive Risk Factors and Breast Cancer Subtypes: A Review of the Literature. *Breast Cancer Res Treat* (2014) 144:1–12. doi: 10.1007/s10549-014-2852-7
11. Yager JD, Davidson NE. Estrogen Carcinogenesis in Breast Cancer. *N Engl J Med* (2006) 354:270–85. doi: 10.1056/NEJMra050776
12. Missmer SA, Eliassen AH, Barbieri RL, et al. Endogenous Estrogen, Androgen, and Progesterone Concentrations and Breast Cancer Risk Among Postmenopausal Women. *J Natl Cancer Inst* (2004) 96:1856–62. doi: 10.1093/jnci/djh336
13. Miyoshi Y, Tanji Y, Taguchi T, Tamaki Y, Noguchi S. Association of Serum Estrone Levels With Estrogen Receptor-Positive Breast Cancer Risk in Postmenopausal Japanese Women. *Clin Cancer Res* (2003) 9:2229–35.
14. Saha T, Makar S, Swetha R, Gutti G, Singh SK. Estrogen Signaling: An Emanating Therapeutic Target for Breast Cancer Treatment. *Eur J Med Chem* (2019) 177:116–43. doi: 10.1016/j.ejmech.2019.05.023
15. Samavat H, Kurzer MS. Estrogen Metabolism and Breast Cancer. *Cancer Lett* (2015) 356(2 Pt A):231–43. doi: 10.1016/j.canlet.2014.04.018
16. Kensler KH, Eliassen AH, Rosner BA, Hankinson SE, Brown M, Tamimi RM. Pre-Diagnostic Sex Hormone Levels and Survival Among Breast Cancer Patients. *Breast Cancer Res Treat* (2019) 174(3):749–58. doi: 10.1007/s10549-018-05121-8
17. Dashti SG, Simpson JA, Karahalios A, Viallon V, Moreno-Betancur M, Gurrin LC, et al. Adiposity and Estrogen Receptor-Positive, Postmenopausal Breast Cancer Risk: Quantification of the Mediating Effects of Fasting Insulin and Free Estradiol. *Int J Cancer* (2020) 146(6):1541–52. doi: 10.1002/ijc.32504
18. Mohammed RH, Lakatua DJ, Haus E, Yasminih WJ. Estrogen and Progesterone Receptors in Human Breast Cancer. Correlation With Histologic Subtype and Degree of Differentiation. *Cancer* (1986) 58:1076–86. doi: 10.1002/1097-0142(19860901)58:5<1076::AID-CNCR2820580516>3.0.CO;2-M
19. Ménard S, Casalini P, Campiglio M, Pupa SM, Tagliabue E. Role of HER2/neu in Tumor Progression and Therapy. *Cell Mol Life Sci* (2004) 61:2965–78. doi: 10.1007/s00018-004-4277-7
20. Krishnamurti U, Silverman JF. HER2 in Breast Cancer: A Review and Update. *Adv Anat Pathol* (2014) 21:100–9. doi: 10.1097/PAP.0000000000000015
21. Cordera F, Jordan VC. Steroid Receptors and Their Role in the Biology and Control of Breast Cancer Growth. *Semin Oncol* (2006) 33:631–42. doi: 10.1053/j.seminoncol.2006.08.020
22. Podo F, Buydens LM, Degani H, Hilhorst R, Klipp E, Gribbestad IS, et al. Triple-Negative Breast Cancer: Present Challenges and New Perspectives. *Mol Oncol* (2010) 4:209–21. doi: 10.1016/j.molonc.2010.04.006
23. Papamitsou T, Toskas A, Papadopoulou K, Sioga A, Lakis S, Chatzistamatiou M, et al. Immunohistochemical Study of Immunological Markers: HLAG, CD16, CD25, CD56, and CD68 in Placenta Tissues in Recurrent Pregnancy Loss. *Histol Histopathol* (2014) 29(8):1047–55. doi: 10.14670/HH-29.1047
24. Goldzieher MA. Treatment of Excessive Growth in the Adolescent Female. *J Clin Endocrinol Metab* (1956) 16:249–55. doi: 10.1210/jcem-16-2-249
25. Ritzen EM, Nilsson O, Grigelioniene G, Holst M, Sävendahl L, Wroblewski J. Estrogens and Human Growth. *J Steroid Biochem Mol Biol* (2000) 74:383–96. doi: 10.1016/S0960-0760(00)00116-3
26. Zhang X, Tworoger SS, Eliassen AH, Hankinson SE. Postmenopausal Plasma Sex Hormone Levels and Breast Cancer Risk Over 20 Years of Follow-Up. *Breast Cancer Res Treat* (2013) 137(3):883–92. doi: 10.1007/s10549-012-239l-z
27. Luo Y, Li HB, Zhang Y, Wu YX, Shen D, Che Y. Combination of Endogenous Stradiol and Adipokine Leptin in Breast Cancer Risk and Prognosis Assessment in Postmenopausal Chinese Women. *Front Endocrinol* (2021) 12:766463. doi: 10.3389/fendo.2021/766463
28. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of Hormone Receptor-Defined Breast Cancer: A Systematic Review of the Literature. *Cancer Epidemiol Biomarkers Prev* (2004) 13:1558–66.
29. Payne SJL, Bowen RL, Jones JL, Wells CA. Predictive Markers in Breast Cancer: The Present. *Histopathology* (2008) 52:82–93. doi: 10.1111/j.1365-2559.2007.02897.x
30. Nadji M, Gomez-Fernandez C, Ganjei-Azar P, Morales AR. Immunohistochemistry of Estrogen and Progesterone Receptors Reconsidered: Experience With 5,993 Breast Cancers. *Am J Clin Pathol* (2005) 123:9–17. doi: 10.1309/4WV79N2GHJ3X1841
31. Rakha EA, El-Sayed ME, Green AR, Paish EC, Powe Dg , Gee J, et al. Biologic and Clinical Characteristics of Breast Cancer With Single Hormone Receptor-Positive Phenotype. *J Clin Oncol* (2007) 25:4772–85. doi: 10.1200/JCO.2007.12.2747
32. Huang HJ, Neven P, Drijkoningen M, Paridaens R, Wildiers H, Limbergen EV, et al. Association Between Tumor Characteristics and HER-2/Neu by Immunohistochemistry in 1,362 Women With Primary Operable Breast Cancer. *J Clin Pathol* (2005) 58:611–21. doi: 10.1136/jcp.2004.022772
33. Martin MB, Saceda M, Lindsey RK. Regulation of Estrogen Receptor Expression in Breast Cancer. *Adv Exp Med Biol* (1993) 330:143–55. doi: 10.1007/978-1-4615-2926-2_11


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 19 July 2022
doi: 10.3389/fonc.2022.772726

# Analysis of the Risk Factors for Elevated D-Dimer Level After Breast Cancer Surgery: A Multicenter Study Based on Nursing Follow-Up Data

*Yanqiu Wang[1], Xi Liang[1]*, Shujun Wang[2]*, Yuying Wang[3]*, Ling Qin[4]*, Danni Chen[5], Yanlin Jiang[6] and Hao Zhang[3]**

[1] Department of Breast Surgery, Second Hospital of Dalian Medical University, Dalian, China, [2] Department of Obstetrics and Gynecology, Second Hospital of Dalian Medical University, Dalian, China, [3] Department of Breast Surgery, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Shenyang, China, [4] Department of Operation Room, Second Hospital of Dalian Medical University, Dalian, China, [5] Department of Neurology, Boao Yiling Life Care Center, Boao, China, [6] Department of Breast Surgery, Affiliated Zhongshan Hospital of Dalian University, Dalian, China

OPEN ACCESS

**Edited by:**
Julio de la Torre,
Comillas Pontifical University, Spain

**Reviewed by:**
Marcus Vetter,
University Hospital of Basel, Switzerland
Hon-Yi Shi,
Kaohsiung Medical University, Taiwan

***Correspondence:**
Xi Liang
ko0313@163.com
Shujun Wang
80510164@qq.com
Yuying Wang
wangyuying8@outlook.com
Ling Qin
765223141@qq.com
Hao Zhang
haozhang840514@163.com

**Specialty section:**
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

**Received:** 08 September 2021
**Accepted:** 21 June 2022
**Published:** 19 July 2022

**Citation:**
Wang Y, Liang X, Wang S, Wang Y, Qin L, Chen D, Jiang Y and Zhang H (2022) Analysis of the Risk Factors for Elevated D-Dimer Level After Breast Cancer Surgery: A Multicenter Study Based on Nursing Follow-Up Data. Front. Oncol. 12:772726. doi: 10.3389/fonc.2022.772726

D-dimer level is often used to assess the severity of trauma as well as the risk of thrombosis. This study investigated the risk factors for high postoperative D-dimer level. This study included a total of 2706 patients undergoing breast cancer surgery to examine the associations between various clinicopathological factors and variation in D-dimer levels. After adjusting for other factors, T stage, neoadjuvant chemotherapy, blood loss, surgery type, diabetes, and elevated leukocyte and neutrophil counts were found to be significant risk factors for D-dimer variation. This study identified several factors associated with elevated D-dimer levels and consequent thrombosis after breast cancer surgery, which may aid in the development of more precise preventive measures and interventions as well as serve as a reference for future research.

**Keywords: D-dimer, breast cancer, surgery, nursing, thrombosis**

## INTRODUCTION

Breast cancer has recently become the most common malignancy worldwide and is also the leading type of cancer in China. With advances in treatment techniques, relatively good therapeutic effects are generally achieved in the treatment of breast cancer (1, 2). Therefore, good survival rates and quality of life are expected in early-stage patients (3, 4). There are relatively few severe complications in the perioperative period of breast cancer surgery, with the most severe being venous thrombosis of the lower extremities and the consequent pulmonary embolism, which often lead to serious damage to health or death of patients and a heavy financial burden (5). In general, a smaller scope of surgery can effectively reduce the occurrence of complications and is indicative of better postoperative breast appearance (6–8). Therefore, breast-conserving surgery has become an increasingly popular approach among patients who meet the relevant indications. The reduced degree of injury provides several benefits, including fewer surgical complications, faster recovery, and increased long-term survival (9–11). However, these methods pose new challenges for the postoperative care of patients with breast cancer. Thus, a comprehensive analysis of the

clinicopathological features and surgical approach of patients is required to assess the degree of trauma and risk of thrombosis.

To maintain normal physiological status, the coagulation system is activated to prevent blood loss in the event of vascular injury. Despite its lack of specificity, an elevated D-dimer level serves as a relatively sensitive biomarker for thrombosis in the circulatory system. Therefore, D-dimer level is often utilized in clinical practice to aid in the diagnosis of venous thromboembolism, deep vein thrombosis, and pulmonary embolism. D-dimer level has also been shown to correlate directly with the degree of trauma, making it an appropriate indicator for assessing injury severity (12, 13). Therefore, when we use D-dimer level as an index to measure the risk of thrombosis, we should realize the limitations of D-dimer as a negative predictive factor for adverse events and pay attention to excluding other influencing factors, such as trauma scope, age, preoperative treatment, disease stage, etc., and analyze the independent risk of different factors under the coexistence of multiple factors. At the same time, in the era of epidemic, the treatment of tumor also has some new challenges. Have patients with COVID-19 affected the coagulation of blood because of pathological changes in the lungs? (14) Whether or not you have ever suffered from COVID-19, will the vaccination affect the hemagglutination state? (15) For tumor patients, their own diseases may bring blood hypercoagulability. At the same time, tumor patients also have the characteristics of relatively old age. In these patients, how to measure the relationship between coagulation indexes and thrombosis risk is also a subject that needs special analysis (16, 17). In order to more accurately understand the potential risk of thrombosis in patients, we should also continuously refine the monitoring process of D-dimer, find the most accurate time point for blood sampling and testing, and develop more biomarkers for modeling and prediction, so as to avoid the influence of multiple confounding factors caused by simple D-dimer (18–21). In a word, under the situation of epidemic situation, aging population and increasing tumor incidence rate, how to give consideration to the treatment effect of tumor and the quality of life of patients, and maximize the net benefit of patients is a subject that needs to be continuously studied. In this context, the present study investigated the role of D-dimer level in thrombosis and injury before and after surgery for the treatment of breast cancer. We aimed to explore independent risk factors for elevated postoperative D-dimer level and the influencing factors of the degree of trauma and risk of thrombosis to provide a basis for the identification of patients who require close monitoring.

# METHODS

## Patients

This study enrolled 2706 patients who underwent breast cancer surgery from 2013-2020, including total mastectomy (glandectomy), and breast-conserving surgery, at the Second Hospital of Dalian Medical University, and the Affiliated Zhongshan Hospital of Dalian University. The inclusion criteria were: 1. The patient was diagnosed with breast cancer and underwent breast cancer surgery, and the time from the last general anesthesia operation was more than one year; 2. Received or not neoadjuvant therapy before operation; 3. 18-75 years old; 4. No distant metastasis; 5. Complete clinicopathological information, especially the test results of D-dimer before and after operation. The exclusion criteria were: 1. Received general anesthesia within one year; 2. The patient was younger than 18 years old or older than 75 years old; 3. There were distant metastatic lesions before operation; 4. The clinicopathological information is incomplete. The clinical, surgical, and pathological findings and all medical data, including age, tumor stage, nodal stage, neoadjuvant chemotherapy, operative time, blood loss, surgery, preoperative and postoperative complications were collected prospectively and recorded in a database.

This study was approved by the Ethics Committee of Second Hospital of Dalian Medical University. All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from all participants.

## Blood Sampling

Blood samples for the determination of pre- and postoperative D-dimer levels were acquired together with the samples used for other hematological tests. Preoperative sampling was usually performed on the second day after admission, approximately 3 days before surgery. Before surgery, in addition to D-dimer, we will detect the patient's blood routine, liver function, renal function, coagulation, blood glucose, blood lipid, blood ions, etc. Postoperative sampling was usually performed 1 day after surgery. After the operation, we will detect the blood routine, blood ions, four items of coagulation, D-dimer, etc.

## Statistical Analyses

Chi-square tests were used to analyze the differences between groups of various D-dimer levels. Correlation analyses were used to identify the influencing factors of D-dimer levels. Multivariate analyses using the ENTER method were conducted to assess the risk factors for increased D-dimer levels. All analyses were performed using IBM SPSS Statistics for Windows, version 23.0. Two-sided P-values <0.05 were considered statistically significant.

# RESULTS

## Patient Characteristics

A total of 13 clinicopathological factors were identified and included in the analysis. The distribution of various clinicopathological factors was subsequently compared between the two groups (pre- and postoperative D-dimer levels). Of these, T stage, neoadjuvant chemotherapy, blood loss, surgery, diabetes, and leukocyte and neutrophil elevation differed significantly between the two D-dimer groups (**Table 1**). The factors with significantly different distributions between the two groups were identified as possible risk factors for D-dimer variation.

**TABLE 1 |** Characteristics of population by D-dimer increase level (n = 2706).

| Characteristics | ≤150 | >150 | p Value |
|---|---|---|---|
| **Age (years)** | | | 0.054 |
| ≤60 | 364 (39) | 749 (43) | |
| >60 | 578 (61) | 1015 (57) | |
| **Pathological tumour stage** (%) | | | <0.001 |
| T1 | 73 (8) | 95 (5) | |
| T2 | 136 (14) | 171 (10) | |
| T3 | 433 (46) | 920 (52) | |
| T4 | 300 (32) | 578 (33) | |
| **Pathological nodal stage** (%) | | | 0.249 |
| N0 | 574 (61) | 1100 (62) | |
| N1 | 249 (26) | 486 (28) | |
| N2 | 85 (9) | 126 (7) | |
| N3 | 34 (4) | 52 (3) | |
| **Neoadjuvant chemotherapy (%)** | | | <0.001 |
| No | 635 (67) | 966 (55) | |
| Yes | 307 (33) | 798 (45) | |
| **Operative time** (%) | | | 0.103 |
| <2h | 216 (23) | 357 (20) | |
| >2h | 726 (77) | 1407 (80) | |
| **Blood loss** | | | <0.001 |
| <100 ml | 588 (72) | 914 (62) | |
| >100 ml | 233 (28) | 567 (38) | |
| **Surgery** | | | <0.001 |
| Total mastectomy | 643 (68) | 929 (53) | |
| BCS + SLNB | 299 (31) | 835 (47) | |
| **Preoperative co-morbidities** | | | |
| Diabetes | 84 (9) | 308 (18) | <0.001 |
| Hypertension | 272 (29) | 490 (28) | 0.546 |
| Cardiac history | 62 (7) | 123 (7) | 0.701 |
| Cerebrovascular disease | 53 (6) | 141 (8) | 0.023 |
| **Postoperative complications** | | | |
| Leukocyte elevation | 49 (5) | 145 (8) | 0.004 |
| Neutrophil elevation | 42 (5) | 170 (10) | <0.001 |

## Correlation Analysis

Spearman correlation analysis showed linear correlations between D-dimer difference and neoadjuvant chemotherapy, T stage, surgery, blood loss, diabetes, leukocyte and neutrophil elevation, and cerebrovascular disease (**Table 2**).

## Risk Factor Analysis

The associations between the possible risk factors and elevated D-dimer level is shown in **Table 3**. After adjusting for the 13 variables, T stage, neoadjuvant chemotherapy, blood loss, surgery type, diabetes, and leukocyte and neutrophil elevation were identified as significant risk factors.

# DISCUSSION

In recent years, increasing attention has been paid to the concept of fast-track surgery, which aims to provide postoperative patients with a variety of integrated treatment approaches to achieve rapid recovery. This leads to the reduction of psychological and organic traumatic stress reactions, which ultimately reduces postoperative complications, shortens the average length of hospital stay, decreases the risk of death, and reduces health care costs (22). However, fast-track surgery is not yet optimized and remains under development. Modifications

**TABLE 2 |** Spearman correlation analysis between clinicopathological features and D-dimer.

| Clinicopathological features | D-dimer ( p; Spearman correlation) |
|---|---|
| Neoadjuvant chemotherapy | <0.001 (0.123) |
| T stage | 0.01 (0.05) |
| Surgery | <0.001 (0.151) |
| Blood loss | <0.001 (0.100) |
| Diabetes | <0.001 (0.116) |
| Leukocyte elevation | 0.004 (0.056) |
| Neutrophil elevation | <0.001 (0.092) |
| Cerebrovascular disease | 0.023 (0.044) |

are also required for specific treatment measures to enhance their suitability for the Chinese population. Therefore, clinicopathological data, surgical information, postoperative complication data, and the prognostic and follow-up information of patients requiring surgery must be collected continuously to perform statistical analysis to aid the development of more reliable and effective diagnostic and treatment modalities for the Chinese population (23, 24).

The present study identified T stage, neoadjuvant chemotherapy, blood loss, surgery type, diabetes, and leukocyte and neutrophil elevation as risk factors for significantly increased D-dimer level.

Our results differ from those of previous studies in that age was not an independent risk factor. Although this is contradictory to the conventional belief that older age is associated with a higher risk of concomitant thrombosis, it suggests that younger patients should also be monitored closely for the occurrence of postoperative venous thrombosis (25–29).

With the increase in the proportion of patients undergoing neoadjuvant chemotherapy, there is a greater need to closely monitor D-dimer level and the possible risk of venous thrombosis (20). During surgery, efforts should also be made to minimize operative time and reduce intraoperative bleeding. For patients in whom the breast and axilla can be preserved, the scope of surgery should also be minimized. To a certain extent, D-dimer level can reflect the degree of damage to the body. Previous studies did not report surgical approach as having a significant effect on D-dimer level; however, its effects have gradually become pronounced with the increasing number of cases (30–32). This may be attributed to the presence of confounding bias among surgical approaches in previous studies, such as the prolonged operative time and intraoperative pathological waiting time for breast-conserving surgery and sentinel lymph node biopsy. Operative time was also not an independent factor due to various confounding factors.

Diabetes mellitus is a known risk factor for thrombosis (33, 34). In particular, the physiological changes following general anesthesia often result in high blood glucose levels, which increase the risk of thrombosis when combined with prolonged bed rest. Thus, careful patient monitoring is required.

Postoperative infection, especially cellular infection that results in elevated neutrophil count, is a risk factor for thrombosis (35–37). It may also exacerbate injury and lead to elevated D-dimer levels. Although the degree of D-dimer elevation does not necessarily correlate with the risk of

**TABLE 3 |** OR for increasing of D-dimer—multivariable analysis (n = 623).

| | Enter method | |
|---|---|---|
| | **OR (95% CI)** | **p** |
| **Age** | 0.906 (0.728-1.127) | 0.374 |
| **Pathological tumor stage** | | 0.002 |
| T1 | Ref | |
| T2 | 1.024 (0.624-1.679) | 0.926 |
| T3 | 1.525 (0.962-2.417) | 0.073 |
| T4 | 1.813 (1.095-3.004) | 0.021 |
| **Pathological nodal stage** | | 0.926 |
| N0 | Ref | |
| N1 | 0.967 (0.762-1.226) | 0.781 |
| N2 | 0.868 (0.613-1.230) | 0.425 |
| N3 | 1.141 (0.626-2.077) | 0.667 |
| **Neoadjuvant chemotherapy** | 2.251 (1.811-2.797) | <0.001 |
| **Operative time** | 0.849 (0.675-1.068) | 0.162 |
| **Blood loss** | 1.686 (1.375-2.067) | <0.001 |
| **Surgery** | 1.676 (1.350-2.082) | <0.001 |
| **Preoperative complications** | | |
| Diabetes | 2.587 (1.933-3.461) | <0.001 |
| Hypertension | 0.928 (0.732-1.175) | 0.533 |
| Cardiac history | 0.852 (0.601-1.208) | 0.369 |
| Cerebrovascular disease | 1.413 (0.961-2.078) | 0.079 |
| **Postoperative complications** | | |
| Leukocyte elevation | 1.840 (1.247-2.715) | 0.002 |
| Neutrophil elevation | 3.364 (2.159-5.241) | <0.001 |

thrombosis and degree of physical injury, measures should still be adopted to prevent postoperative infections such as drain-related, wound, and urinary tract infections.

A high postoperative D-dimer level may correspond to more severe physical injury and a higher risk of postoperative thrombosis. Our findings indicated that, despite advances in diagnosis and treatment, it is still critical for researchers to collect data on basic patient information, records of previous treatment, and the prevention and treatment of perioperative complications.

## CONCLUSIONS

The results of the present study revealed multiple risk factors that may cause a significant increase in D-dimer level in the postoperative period. These findings suggest the need to pay particular attention to these patients during the perioperative period, adopt adequate preventive measures, and conduct relevant research.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

This study was reviewed and approved by Second Hospital of Dalian Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

LQ, YQW, YYW and XL participated in the study design and manuscript drafting. SW, HZ, and YJ participated in the study design and manuscript drafting. DC, HZ, and YJ participated in the statistical analysis and manuscript drafting. All authors contributed to the article and approved the submitted version.

## FUNDING

This research was funded by Dalian Medical Science Research Project (1612023).

## REFERENCES

1. Ginsburg O, Badwe R, Boyle P, Derricks G, Dare A, Evans T, et al. Changing Global Policy to Deliver Safe, Equitable, and Affordable Care for Women's Cancers. *Lancet* (2017) 389(10071):871–80. doi: 10.1016/S0140-6736(16)31393-9
2. Li T, Mello-Thoms C, Brennan PC. Descriptive Epidemiology of Breast Cancer in China: Incidence, Mortality, Survival and Prevalence. *Breast Cancer Res Treat* (2016) 159(3):395–406. doi: 10.1007/s10549-016-3947-0
3. Nardin S, Mora E, Varughese FM, D'Avanzo F, Vachanaram AR, Rossi V, et al. Breast Cancer Survivorship, Quality of Life, and Late Toxicities. *Front Oncol* (2020) 10:864. doi: 10.3389/fonc.2020.00864

4. Invernizzi M, de Sire A, Lippi L, Venetis K, Sajjadi E, Gimigliano F, et al. Impact of Rehabilitation on Breast Cancer Related Fatigue: A Pilot Study. *Front Oncol* (2020) 10:556718. doi: 10.3389/fonc.2020.556718
5. Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *CA Cancer J Clin* (2016) 66(1):43–73. doi: 10.3322/caac.21319
6. Yan Z, Wang Q, Sun X, Ban B, Lu Z, Dang Y, et al. OSbrca: A Web Server for Breast Cancer Prognostic Biomarker Investigation With Massive Data From Tens of Cohorts. *Front Oncol* (2019) 9:1349. doi: 10.3389/fonc.2019.01349
7. Invernizzi M, Corti C, Lopez G, Michelotti A, Despini L, Gambini D, et al. Lymphovascular Invasion and Extranodal Tumour Extension are Risk Indicators of Breast Cancer Related Lymphoedema: An Observational Retrospective Study With Long-Term Follow-Up. *BMC Cancer* (2018) 18 (1):935. doi: 10.1186/s12885-018-4851-2
8. Rockson SG. Lymphedema After Breast Cancer Treatment. *N Engl J Med* (2018) 379(20):1937–44. doi: 10.1056/NEJMcp1803290
9. Lee GK, Sheckter CC. Breast Reconstruction Following Breast Cancer Treatment-2018. *JAMA* (2018) 320(12):1277–8. doi: 10.1001/jama.2018.12190
10. Cutress RI, McIntosh SA, Potter S, Goyal A, Kirwan CC, Harvey J, et al. Opportunities and Priorities for Breast Surgical Research. *Lancet Oncol* (2018) 19(10):e521–33. doi: 10.1016/S1470-2045(18)30511-4
11. Mamtani A, Morrow M. Why Are There So Many Mastectomies in the United States? *Annu Rev Med* (2017) 68:229–41. doi: 10.1146/annurev-med-043015-075227
12. Dong Y, Duan G, Wang H, Ru J, Cui Y. A Cohort Study of Rivaroxaban Combined With D-Dimer Dynamic Monitoring in the Prevention of Deep Venous Thrombosis After Knee Arthroplasty. *Comput Math Methods Med* (2022) 2022:3965039. doi: 10.1155/2022/3965039
13. Alharbi OA, Alahmadi KO. The Diagnostic Utility of Unenhanced Computed Tomography of the Brain and D-Dimer Levels in Acute Cerebral Venous Sinus Thrombosis: A Quantitative Study. *J Clin Imaging Sci* (2022) 12:15. doi: 10.25259/JCIS_76_2021
14. Kazantsev AN, Karkayeva MR, Tritenko AP, Korotkikh AV, Zharova AS, Chernykh KP, et al. Carotid Enadrterectomy For Internal Carotid Thrombosis In Patients With Covid-19. *Curr Probl Cardiol* (2022) 13:101252. doi: 10.1016/j.cpcardiol.2022.101252
15. Brito-Dellan N, Tsoukalas N, Font C. Thrombosis, Cancer, and COVID-19. *Support Care Cancer* (2022) 14:1–10. doi: 10.1007/s00520-022-07098-z
16. Hayashida K, Kawabata Y, Saito K, Fujita S, Choe H, Kato I, et al. Prevalence and Risk Factors of Preoperative Venous Thromboembolism in Patients With Malignant Musculoskeletal Tumors: An Analysis Based on D-Dimer Screening and Imaging. *Thromb J* (2022) 20(1):22. doi: 10.1186/s12959-022-00382-2
17. Invernizzi M, Michelotti A, Noale M, Lopez G, Runza L, Giroda M, et al. Breast Cancer Systemic Treatments and Upper Limb Lymphedema: A Risk-Assessment Platform Encompassing Tumor-Specific Pathological Features Reveals the Potential Role of Trastuzumab. *J Clin Med* (2019) 8(2):138. doi: 10.3390/jcm8020138
18. Xu L, Ji C, Miao X, Ge J, Li F, Xu C, et al. Combination of Circulating miR-125a-5p, miR-223-3p and D-Dimer as a Novel Biomarker for Deep Vein Thrombosis. *Am J Med Sci* (2022) S0002-9629(22):00226-9. doi: 10.1016/j.amjms.2022.04.033
19. Zhang L, He M, Jia W, Xie W, Song Y, Wang H, et al. Analysis of High-Risk Factors for Preoperative DVT in Elderly Patients With Simple Hip Fractures and Construction of a Nomogram Prediction Model. *BMC Musculoskelet Disord* (2022) 23(1):441. doi: 10.1186/s12891-022-05377-8
20. Akagawa M, Kijima H, Kimura Y, Saito H, Saito K, Wakabayashi I, et al. Fibrin Monomer Complex on Postoperative Day 1 is Correlated With the Volume of Deep Vein Thrombosis After Knee Surgery. *J Exp Orthop* (2022) 9 (1):47. doi: 10.1186/s40634-022-00482-y
21. Wang X, Jiang Z, Li Y, Gao K, Gao Y, He X, et al. Prevalence of Preoperative Deep Venous Thrombosis (DVT) Following Elderly Intertrochanteric Fractures and Development of a Risk Prediction Model. *BMC Musculoskelet Disord* (2022) 23(1):417. doi: 10.1186/s12891-022-05381-y
22. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. *JAMA Surg* (2017) 152(3):292–8. doi: 10.1001/jamasurg.2016.4952
23. Kim L, McGee L, Tomczyk S, Beall B. Biological and Epidemiological Features of Antibiotic-Resistant Streptococcus Pneumoniae in Pre- and Post-Conjugate Vaccine Eras: A United States Perspective. *Clin Microbiol Rev* (2016) 29(3):525–52. doi: 10.1128/CMR.00058-15
24. Wainwright TW, Immins T, Middleton RG. Enhanced Recovery After Surgery (ERAS) and its Applicability for Major Spine Surgery. *Best Pract Res Clin Anaesthesiol* (2016) 30(1):91–102. doi: 10.1016/j.bpa.2015.11.001
25. Johnson ED, Schell JC, Rodgers GM. The D-Dimer Assay. *Am J Hematol* (2019) 94(7):833–9. doi: 10.1002/ajh.25482
26. Linkins LA, Takach Lapner S. Review of D-Dimer Testing: Good, Bad, and Ugly. *Int J Lab Hematol* (2017) 39 Suppl 1:98–103. doi: 10.1111/ijlh.12665
27. Olaf M, Cooney R. Deep Venous Thrombosis. *Emerg Med Clin North Am* (2017) 35(4):743–70. doi: 10.1016/j.emc.2017.06.003
28. Hayakawa M, Maekawa K, Kushimoto S, Kato H, Sasaki J, Ogura H, et al. High D-Dimer Levels Predict a Poor Outcome in Patients With Severe Trauma, Even With High Fibrinogen Levels on Arrival: A Multicenter Retrospective Study. *Shock* (2016) 45(3):308–14. doi: 10.1097/SHK.0000000000000542
29. Yumoto T, Naito H, Yamakawa Y, Iida A, Tsukahara K, Nakao A. Venous Thromboembolism in Major Trauma Patients: A Single-Center Retrospective Cohort Study of the Epidemiology and Utility of D-Dimer for Screening. *Acute Med Surg* (2017) 4:394–400. doi: 10.1002/ams2.290
30. Lin Y, Liu Z, Qiu Y, Zhang J, Wu H, Liang R, et al. Clinical Significance of Plasma D-Dimer and Fibrinogen in Digestive Cancer: A Systematic Review and Meta-Analysis. *Eur J Surg Oncol* (2018) 44(10):1494–503. doi: 10.1016/j.ejso.2018.07.052
31. Greenberg CS. The Role of D-Dimer Testing in Clinical Hematology and Oncology. *Clin Adv Hematol Oncol* (2017) 15(8):580–3.
32. Favresse J, Lippi G, Roy PM, Chatelain B, Jacqmin H, Ten Cate H, et al. D-Dimer: Preanalytical, Analytical, Postanalytical Variables, and Clinical Applications. *Crit Rev Clin Lab Sci* (2018) 55(8):548–77. doi: 10.1080/10408363.2018.1529734
33. Westein E, Hoefer T, Calkin AC. Thrombosis in Diabetes: A Shear Flow Effect? *Clin Sci (Lond)* (2017) 131(12):1245–60. doi: 10.1042/CS20160391
34. Pechlivani N, Ajjan RA. Thrombosis and Vascular Inflammation in Diabetes: Mechanisms and Potential Therapeutic Targets. *Front Cardiovasc Med* (2018) 5:1. doi: 10.3389/fcvm.2018.00001
35. Kapoor S, Opneja A, Nayak L. The Role of Neutrophils in Thrombosis. *Thromb Res* (2018) 170:87–96. doi: 10.1016/j.thromres.2018.08.005
36. Hisada Y, Mackman N. Cancer-Associated Pathways and Biomarkers of Venous Thrombosis. *Blood* (2017) 130(13):1499–506. doi: 10.1182/blood-2017-03-743211
37. Li W, Tang Y, Song Y, Chen SH, Sisliyan N, Ni M, et al. Prognostic Role of Pretreatment Plasma D-Dimer in Patients With Solid Tumors: A Systematic Review and Meta-Analysis. *Cell Physiol Biochem* (2018) 45(4):1663–76. doi: 10.1159/000487734


**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 02 August 2022
DOI 10.3389/fonc.2022.844926



OPEN ACCESS

EDITED BY
Julio de la Torre,
Comillas Pontifical University, Spain

REVIEWED BY
Mitasha Singh,
ESIC Medical College, India
Teresa Young,
East and North Hertfordshire NHS Trust, United Kingdom

*CORRESPONDENCE
Yul Ha Min
yulhamin@gmail.com

SPECIALTY SECTION
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

RECEIVED 29 December 2021
ACCEPTED 14 July 2022
PUBLISHED 02 August 2022

CITATION
Sung S, Min YH, Park SK and Lee SB (2022) Hot flushes and sweating, sleep problems, joint and muscular discomfort, and physical and mental exhaustion in breast cancer survivors during the first 24 months of tamoxifen therapy: a prospective observational study.
*Front. Oncol.* 12:844926.
doi: 10.3389/fonc.2022.844926



# Hot flushes and sweating, sleep problems, joint and muscular discomfort, and physical and mental exhaustion in breast cancer survivors during the first 24 months of tamoxifen therapy: a prospective observational study

Sumi Sung[1], Yul Ha Min[2]*, Seul Ki Park[3] and Sae Byul Lee[4]

[1]College of Nursing, Seoul National University, Seoul, South Korea, [2]College of Nursing, Kangwon National University, Kangwon-do, South Korea, [3]Department of Nursing, Daejeon University, Daejeon, South Korea, [4]Division of Breast Surgery, Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

**Purpose:** This study aimed to explore symptom trajectories over 24 months for hot flushes and sweating, sleep problems, joint and muscular discomfort, and physical and mental exhaustion experienced by premenopausal women diagnosed with tamoxifen-treated breast cancer.

**Methods:** A total of 104 patients participated in the study. The menopausal symptoms were examined using the Menopausal Rating Scale at baseline, 3–6, 12, and 18–24 months after initiating tamoxifen. The changes over four time points were analyzed using repeated measures analysis of variance. The chi-square test was used to examine the differences between "no symptom-to-mild" and "moderate-to-extremely severe" 3–6 months after initiating tamoxifen according to the patients' chemotherapy treatment experiences.

**Results:** All menopausal symptoms occurred in > 70% of patients with breast cancer and persisted until 24 months. More than 50% of patients experienced four menopausal symptoms, with at least two at a serious severity level after initiating tamoxifen. Hot flushes and sweating occurred in the highest number of patients, recording high scores. Sleep problems and physical and mental exhaustion exhibited relatively high scores, even before tamoxifen initiation. There were significant changes over four time points in all symptoms. Young patients aged < 40 years experienced more severe sleep problems, and patients who had previously received chemotherapy experienced more severe joint and muscular discomfort.

**Conclusions:** This study's findings may assist in alerting healthcare providers to menopausal symptoms that develop during tamoxifen therapy and the need for early and active intervention to minimize symptom occurrence and distress.

KEYWORDS

adjuvant endocrine therapy, breast cancer, tamoxifen, signs and symptoms, premenopause

## Introduction

Breast cancer (BC) is the most common cancer among Korean women. A total of 23,647 new BC patients were recorded in 2018 in Korea, and the incidence has continuously increased since 1999, with an average annual increase rate of 4.6% (1). Over 75% of these BCs are estrogen receptor positive, and they are amenable to treatment with adjuvant endocrine therapy (AET). There are two types of AET treatment, tamoxifen (TAM) and aromatase inhibitors (AIs). Among them, TAM has historically been prescribed for ≥ 5 years in premenopausal women with estrogen receptor-positive BC, whereas AIs have been prescribed for postmenopausal women. Tamoxifen therapy has resulted in decreased BC recurrence and mortality rates by 39% and 31%, respectively (2–5).

Current guidelines recommend that BC survivors extend adjuvant TAM therapy from 5 to 10 years to prevent recurrence and increase overall survival (3, 5). This increase in treatment duration implies that increasing numbers of women may be suffering from several menopausal symptoms as the most common side effects of TAM (6). Among them, hot flushes and sweating (HFS), sleep problems (SP), joint and muscular discomfort (JMD), and physical and mental exhaustion (PME) were reported to occur in most patients with BC taking TAM (7–10). These symptoms have been found to develop in Korean patients with BC (11). Despite not being life threatening, these symptoms reportedly impact negatively on patients' quality of life and undermine TAM adherence (9, 12).

One of the key menopausal-symptom treatments, hormone replacement therapy, is contraindicated in BC survivors due to a potentially increased risk of cancer recurrence (10). Thus, non-hormonal strategies or non-pharmacological therapies have been preferred for of menopausal-symptom treatment in patients with BC (13, 14). To identify interventions that ameliorate symptoms and provide better support throughout a patient's treatment journey, it is important to understand the patients' menopausal symptoms and symptom trajectories during TAM therapy. Healthcare providers can better predict the timing of their patient's menopausal symptoms and concentrate on caring for patients at risk of elevated symptom burden.

Various studies have investigated the menopausal symptoms experienced by patients with BC taking AET. However, previous studies focused on identifying AET-related symptoms with the highest occurrence, intensity, and distress, including cramps, hot flashes, fatigue, eye irritation, and heart discomfort (15–17). Moreover, most research focused on AI-related symptoms rather than those associated with TAM (7). Even if the study focused on TAM-related symptoms, most research has been limited to cross-sectional studies (9, 10, 18, 19). Relevant longitudinal or cohort studies are limited; hence, the changes in symptoms over time have not been fully elucidated.

In addition, chemotherapy has been known to produce a temporary or permanent menopausal status in premenopausal women. Young women receiving adjuvant chemotherapy are known to experience premature menopause, resulting in increased and occasionally abrupt onset of menopausal symptoms (20). These symptoms may prompt young women undergoing chemotherapy to seek treatment for the prevention or amelioration of symptoms associated with TAM-therapy initiation. Most Korean women are diagnosed with BC in their early 40s resulting in > 50% of them being in a premenopausal state (11). Therefore, it is necessary to determine whether menopausal symptoms appear or worsen after TAM initiation in Korean premenopausal women with BC who have already received chemotherapy.

Therefore, this study aimed to explore symptom trajectories over 24 months of four menopausal symptoms, including HFS, SP, JMD, and PME, experienced by premenopausal women diagnosed with BC taking TAM and determine the incidence of menopausal symptoms in patients who would have already undergone chemotherapy upon initiating TAM.

## Materials and methods

### Study design

This was a prospective observational study.

### Participants and procedure

Between November 2016 and April 2017, 556 consecutive women with histologically confirmed BC at Asan Medical Center

were screened for eligibility upon admission for surgery. Inclusion criteria were as follows: cases with in situ, stage I, II, or III hormone receptor-positive BC; age at diagnosis ≥ 20 years; and definitive surgery followed by AET, irrespective of chemotherapy. Women with distant metastases at diagnosis (stage IV BC); local or regional recurrent tumors; or medical history of psychiatric or neurologic illness were excluded. The detailed sampling and attrition process has been described in a previous study (21). Among 370 eligible patients, 210 consented to participate in this study (137 declined to participate, and 23 could not be contacted). Among the 210 patients, 107 were excluded (90 withdrew their consent during the study, 8 were lost to follow-up, 2 stopped AET, and 7 developed recurrent BC during the first 24 months of AET). During the hospital stay after breast cancer surgery, subjects were contacted by a clinical research nurse. After obtaining consent, patients completed paper-based questionnaires at the first visit (Time 1) to the clinic after discharge and at 3,6,12, and 18 months visit to the clinic after initiating TAM.

In this study, out of the 210 patients, we selected 135 patients who have prescribed TAM and were pre-menopausal. Those who do not meet the menopause criteria were classified as pre-menopause. Criteria for determining menopause included any of the following: age ≥ 60 years or age < 60 years with amenorrhea for ≥ 12 months in the absence of prior chemotherapy or receipt of TAM and Follicle-stimulating hormone (FSH) in the post-menopausal range (≥ 30 mIU/ml) (5). We classified data collected at 3 and 6 months as Time 2 and that at 18 and 24 months as Time 4. Therefore, Time 1 represents the data collected upon TAM initiation at baseline, and Time 2 represents data at 3–6 months, Time 3 at 12 months, and Time 4 at 18–24 months after initiating TAM. Finally, 104 patients without missing data were used in the analysis.

At Time 1, we collected patients' general characteristics from electronic medical records with their consent, including age, educational level, employment status, prior history of cancer, family history of cancer, cancer stage, and treatment process (type of surgery, chemotherapy, and radiation therapy).

## Measures

HFS, SP, JMD, and PME symptoms were measured using the Korean version of the menopause rating scale (MRS) (22). The scale comprises three dimensions: somato-vegetative, psychological, and urogenital symptoms, with 11 items. Each item was scored using the following 5-point Likert scale: no symptom = 0, mild = 1, moderate = 2, severe = 3, and extremely severe = 4. A higher total score indicated greater self-reported menopausal symptoms. The scale's Cronbach's $\alpha$ was 0.88.

We assessed adherence to TAM. Patients were asked to rate their adherence rates from 0% to 100% from the last prescription date to the date of reporting medication adherence from Time 2 to Time 4. A 100% rating meant that the patient had taken medication every day, and a 0% rating meant that the patient had not taken any medication on any day.

## Statistical analysis

Statistical analyses were performed using SPSS software (version 26.0; SPSS Inc., Chicago, IL, USA). Participant characteristics were analyzed using descriptive analysis. Furthermore, we analyzed the proportion of patients reporting a score of =1 and ≥2 for each of the four symptoms and the number of patients according to the number of symptoms reporting a score of ≥1 and ≥2 over the four time points using descriptive analysis. Symptom changes on the four time points and interaction effects between participant characteristics and symptoms were analyzed using repeated measures analysis of variance (ANOVA), including the Bonferroni adjustment in the *post-hoc* analysis. Furthermore, the chi-square test was used to evaluate the differences between "no symptom to mild" and "moderate-to-extremely severe" at Time 2, according to the chemotherapy treatment experiences of patients who reported a "no symptom or mild" score at Time 1.

# Results

Table 1 presents an overview of the participants' characteristics. A total of 104 premenopausal patients diagnosed with BC and receiving TAM therapy were included in this study. The mean age was 43.5 ± 6.9 years, and 79.8% of the patients were aged > 40 years. Approximately 60% of them had a university education or above (64.4%), and 55.8% were employed. A high percentage of patients did not have prior (95.2%) or family (67.3%) history of cancer. Most patients were diagnosed with stage I, II, or III (81.7%), and 83.7% underwent conservation surgery. In the course of their treatment, 32.7% and 86.5% of patients received chemotherapy and radiation therapy, respectively. The overall patients' TAM adherence was highest at Time 2 with an average of 96.2% (median of 100%) and the lowest at Time 3 with an average of 91.9% (median of 99%).

Figure 1 describes the proportion of patients reporting "mild" and "moderate-to-extremely severe" MRS scores for HFS, SP, JMD, and PME symptoms over four time points. All four symptoms were reported in > 70% patients after initiating TAM from Time 2 to Time 4. HFS exhibited the greatest increase, from 38.5% at Time 1 to 86.5% at Time 2. The proportion of patients with "moderate-to-extremely severe" MRS scores increased from 53.8% at Time 2 to 58.7% at Time 4. SP and PME demonstrated a high proportion from 67.3% and 73.1% at Time 1 compared to the other two symptoms.

Figure 2 presents the number of patients according to the number of symptoms reporting "mild-to-extremely severe" (≥1) and "moderate-to-extremely severe" (≥2) scores over the four time points. The number of patients who scored ≥ 1 for all four symptoms were 19 (18.3%), 56 (53.8%), 61 (58.7%), and 60 (57.7%) at Times 1, 2, 3, and 4, respectively. The number of patients who scored ≥1 for all four symptoms at Time 1

TABLE 1 Overview of participant characteristics.

| Characteristics | | n (%) or Mean (SD) |
|---|---|---|
| Age (years) | | 43.5 (6.9) |
| | < 40 | 21 (20.0) |
| | ≥ 40 | 83 (79.8) |
| Education level | High school or below | 37 (35.6) |
| | University and above | 67 (64.4) |
| Employment status | Unemployed | 46 (44.2) |
| | Employed | 58 (55.8) |
| Prior history of cancer | No | 99 (95.2) |
| | Yes | 5 (4.8) |
| Family history of cancer | No | 70 (67.3) |
| | Yes | 34 (32.7) |
| Cancer stage | In situ | 19 (18.3) |
| | Invasive (Stage I, II, or III) | 85 (81.7) |
| Type of surgery | Mastectomy | 17 (16.3) |
| | Conservation | 87 (83.7) |
| Chemotherapy | Not done | 70 (67.3) |
| | Done | 34 (32.7) |
| Radiation therapy | Not done | 14 (13.5) |
| | Done | 90 (86.5) |
| Adherence to TAM (%) | Time 2 | 96.2 (14.1) |
| | Time 3 | 91.9 (21.8) |
| | Time 4 | 95.0 (11.6) |

increased approximately 3 times at Time 2 and remained constant until Time 4. Approximately 55% of patients taking TAM experienced four mild-to-extremely severe symptoms simultaneously after taking TAM.

The number of patients with scores ≥ 2 for two or more symptoms were 36 (34.6%), 57 (54.8%), 56 (53.9%), and 56 (53.9%) at Times 1, 2, 3, and 4, respectively. The number of patients with scores ≥ 2 for at least two symptoms at Time 1 increased approximately 1.5 times at Time 2 and remained constant until Time 4. Approximately 50% of patients taking TAM experienced two or more symptoms after taking TAM.

Table 2 presents the repeated measures ANOVA results with a Greenhouse-Geisser correction for the four menopausal symptoms at the four time points. There were significant changes in all symptoms: HFS ($p$<.001), SP ($p$<.001), JMD ($p$<.001), and PME ($p$=.004). Since initiating TAM, HFS exhibited the highest mean scores. SP showed the highest at Time 2, JMD at Time 3, and PME at Time 4. *Post hoc* analysis


FIGURE 1
Proportion of patients reporting "mild" and "moderate-to-extremely severe" scores for HFS, SP, JMD, and PME symptoms.

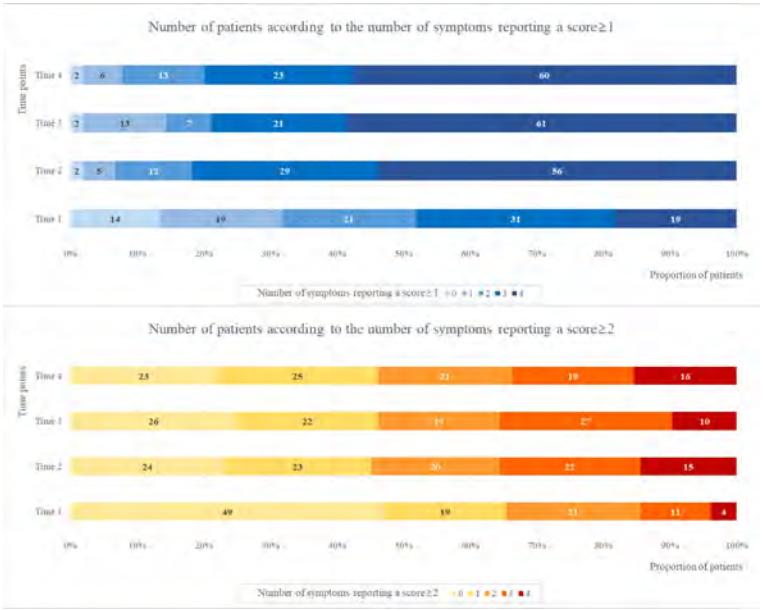



FIGURE 2
The number of patients according to the number of symptoms reporting a score ≥1 and ≥2 at four time points.

with a Bonferroni adjustment revealed that HFS and JMD were statistically significantly increased from Time 1 to Time 2 ($p$<.001), 3 ($p$<.001), and 4 ($p$<.001). SP were statistically significantly increased from Time 1 to Time 2 ($p$=.004) and PME were statistically significantly increased from Time 1 to Time 2 ($p$=.026) and 4 ($p$=.023).

Table 3 presents the interaction effects of participant characteristics on patient-reported symptoms at the four time points. There were statistically significant interaction effects between age and time on SP change ($p$=.019). Patients aged < 40 years demonstrated significantly higher SP scores than those aged > 40 years after initiating TAM therapy. There were significant interaction effects between chemotherapy and time on JMD change ($p$=.025). Patients who had undergone chemotherapy exhibited significantly higher JMD scores than those who had not over the four time points.

Table 4 presents the differences in menopausal-symptom scores at Time 2 according to the chemotherapy treatment experiences of patients who reported "no symptom-to-mild" at Time 1. The results revealed no significant differences between "no symptom-to-mild" and "moderate-to-extremely severe" at Time 2 according to patients' chemotherapy-treatment experiences. However, among patients who had undergone chemotherapy, 56.5% and 43.5% who either did not or mildly experienced HFS and JMD at Time 1 experienced "moderate-to-extremely severe" symptoms at Time 2, respectively.

## Discussion

This study's findings provide 24-month trajectories of four menopausal symptoms, including HFS, SP, JMD, and PME, experienced by premenopausal women diagnosed with BC taking TAM in Korea. This study further provides longitudinal symptom trends of BC in Korean women, with BC incidence being higher in the early 40s and > 50% of patients being premenopausal women, whereas in western countries, BC incidence is predominantly in the 50s (11).

In this study, patient adherence to TAM was found to be relatively high (> 91%), which is consistent with a previous study

TABLE 2 Symptom scores at four time points.

| Menopausal symptoms | Time 1 | Time 2 | Time 3 | Time 4 | F | *p* |
|---|---|---|---|---|---|---|
| Hot flushes and sweating | 0.64 | 1.71 | 1.52 | 1.77 | 47.731 | <.001 |
| Sleep problems | 1.17 | 1.55 | 1.39 | 1.40 | 4.435 | <.001 |
| Joint and muscular discomfort | 0.72 | 1.27 | 1.44 | 1.31 | 13.824 | <.001 |
| Physical and mental exhaustion | 1.18 | 1.48 | 1.38 | 1.51 | 4.711 | .004 |

TABLE 3 Interaction effects of participant characteristics on patient-reported menopausal symptoms over four time points.

| Symptoms | Characteristics | | Time 1 | Time 2 | Time 3 | Time 4 | F | *p* |
|---|---|---|---|---|---|---|---|---|
| Sleep problems | Age | < 40 | 1.05 | 1.90 | 1.57 | 1.90 | 3.496 | .019 |
| | | ≥ 40 | 1.20 | 1.46 | 1.35 | 1.28 | | |
| Joint and muscular discomfort | Chemotherapy | Done | 1.06 | 1.76 | 1.56 | 1.32 | 3.169 | .025 |
| | | Not done | 0.56 | 1.03 | 1.39 | 1.30 | | |

TABLE 4 Menopausal-symptom scores at Time 2 according to chemotherapy in patients who reported "no symptom-to-mild" scores at Time 1.

| Symptoms | Chemotherapy | MRS scores in Time 2 | | $\chi^2$ | *p* |
|---|---|---|---|---|---|
| | | 0–1 | 2–4 | | |
| Hot flushes and sweating | Done | 10 (43.5) | 13 (56.5) | 1.006 | .316 |
| | Not done | 34 (55.7) | 27 (44.3) | | |
| Sleep problems | Done | 15 (78.9) | 4 (21.1) | 1.090 | .296 |
| | Not done | 33 (66.0) | 17 (34.0) | | |
| Joint and muscular discomfort | Done | 13 (56.5) | 10 (43.5) | 3.449 | .063 |
| | Not done | 47 (77.0) | 14 (23.0) | | |
| Physical and mental exhaustion | Done | 10 (66.7) | 5 (33.3) | 0.326 | .568 |
| | Not done | 31 (58.5) | 22 (41.5) | | |

Data are presented as number of patients (%).

that reported > 94% of Korean patients with BC (21), although up to 50% of patients with BC are generally known not to take TAM for the full duration (23). A previous study has suggested that this result is due to the ceiling effect. In this study, as TAM adherence was high, menopausal symptoms, which were side effects of TAM, were also prevalent in many patients from 3 months to 24 months after initiating TAM administration. All four menopausal symptoms were reported in > 70% of patients with BC after initiating TAM and persisted until 24 months. More than 50% of patients experienced four menopausal symptoms, with at least two at a serious severity level 3–6 months after initiating TAM.

HFS occurred in > 80% of patients after initiating TAM, consistent with previous studies in which TAM-prescribed patients with BC patients had a prevalence of approximately 80% (10, 24). We found that the proportion of patients and mean scores exhibited the greatest increase at 3–6 months after initiating TAM. These increases did not continue beyond 24 months; however, they seemed consistent up to 24 months after taking TAM, indicating that HFS persists for a long time. Among the four menopausal symptoms, HFS symptom intensity was found to be predominant. We also found that > 47% of patients experienced moderate-to-extremely severe symptoms after taking TAM, and this proportion increased to > 55% at 18–24 months after initiating TAM, a figure that was slightly lower than the 60% reported in previous studies on patients with BC patients taking TAM (10, 25). This paper adds the following new information: among patients who have no or mild HFS before commencing TAM, > 55% of those who had undergone chemotherapy deteriorated to "moderate-to-extremely severe" at 3–6 months after initiating TAM. This result may provide evidence that corroborates previous research in which HFS and chemotherapy were not associated with postmenopausal women but possibly with premenopausal women (10). HFS has been found to be the greatest factor for intentional non-adherence to AET as well as negatively affect the quality of life of women with BC (25, 26). When prescribing TAM in clinical practice, it is necessary to consider the possibility of HFS occurrence in most patients, and that > 50% of these patients experience severe symptoms, especially in those who would have undergone chemotherapy.

JMD occurred in > 70% of patients after taking TAM, consistent with previous studies on TAM-prescribed patients with BC that indicated a prevalence of approximately 70% (20). We found a significant interaction effect between chemotherapy and time on JMD change. Patients who underwent chemotherapy exhibited higher JMD scores from baseline than those who did not undergo chemotherapy, and they experienced more amplified JMD after commencing TAM treatment. Even among patients with no or mild JMD, > 40% of those who underwent chemotherapy have been shown to experience a worsening of symptoms 3–6 months after initiating TAM, a figure that is approximately twice that of those who have never undergone chemotherapy. This study's results emerged due to the fact that various types of chemotherapy cause JMD (27–29), and the symptoms apparently worsened as TAM therapy was initiated. JMD is known to have a significant impact on patient

quality of life (30, 31), suggesting that active medical intervention is required.

Interestingly, SP and PME occurred in > 60% patients from baseline and persisted until 24 months after TAM. These two symptoms have been known to worsen with the initiation of chemotherapy or radiation therapy and were cumulative over the treatment course (32–34). Previous studies have already demonstrated that SP and PME are correlated (19, 35, 36). Thus, the reason underlying the high proportions and mean scores of SP and PME from baseline seems to be the patients' treatment history, such as previous chemotherapy, radiation therapy, or surgery, among others.

Regarding SP, we found interaction effects between age and time on change. Patients aged < 40 years were found to experience greater SP than those aged > 40 years. Our results conflict with those of previous studies, showing solid evidence that sleep is more fragmented as we age, and that increasing age is associated with poorer sleep (37, 38). The reason this conflict exists is probably that younger women are more likely to present advanced disease and/or undergo aggressive treatment regimens (39), both of which potentially lead to severe SP.

This study has limitations. First, patients in this study were recruited from one tertiary hospital in Seoul, Korea, limiting the generalizability of the findings. Second, sample bias is possible because missing data were excluded. Third, medication TAM adherence and the four menopausal symptoms were assessed using patients' self-reports, which are not exempt from self-presentation or memory bias, thus leading to inaccurate estimations of actual adherence and symptom changes (40). Fourth, although healthcare providers provided further interventions such as drug therapy, or consultation with proper specialists according to the symptom severity complained of by the patients with BC taking AET, these interventions were not considered in the analysis of this study.

## Conclusion

The present study investigated 24-month trajectories of four menopausal symptoms experienced by premenopausal women diagnosed with BC taking TAM in Korea. After initiating TAM therapy, all menopausal symptoms occurred in > 70% of BC patients. Patient symptoms increased at 3–6 months and persisted until 24 months after initiating TAM. More than 50% of patients experienced four menopausal symptoms, with at least two at a serious severity level. HFS occurred in the highest number of patients with high scores. SP and PME demonstrated relatively high scores, even before initiating TAM therapy. Young patients aged < 40 years experienced more severe SP than those aged > 40 years. Patients who had previously undergone chemotherapy experienced JME at a more severe and faster rate than those who had never undergone chemotherapy over the four time points. The present findings may assist in alerting healthcare providers to menopausal symptoms during TAM therapy and the need for early and active intervention to minimize symptom occurrence and distress. Appropriate interventions to manage SP in young women aged < 40 years and JMD in those who would have undergone chemotherapy should be implemented when initiating TAM. In particular, in the case of HFS and JMD, even if patients who have already undergone chemotherapy experience no symptoms before initiating TAM, severe symptoms may appear after TAM is initiated; therefore, active intervention is necessary. Furthermore, healthcare providers should be aware that patients may have high underlying SP and PMEs even before initiating TAM.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Asan Medical Center (2016-0351 and 2018-1249). The patients/participants provided their written informed consent to participate in this study.

## Author contributions

Conceptualization: SS, YHM, SKP, and SBL; Methodology: SS, YHM, and SKP; Formal analysis and investigation: SS, YHM, and SKP; Writing—original draft preparation: SS; Writing—review and editing: SS, YHM, SKP, and SBL; Funding acquisition: YHM; Final approval of manuscript: SS, YHM, SKP, and SBL. All authors contributed to the article and approved the submitted version.

## Funding

This work was supported by the National Research Foundation (NRF) of Korea grant funded by the Korean government (Grant number NRF-2018R1A1A3A04076879).

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## References

1. Korea Central Cancer Registry KCC. *2018 national cancer registry statistics*. Goyang-si Gyeonggi-do: National Cancer Information Center (2018).

2. Harrell JC, Ww D, Harvell DME, Pinto M, Jedlicka P, Sartorius CA, et al. Estrogen insensitivity in a model of estrogen receptor positive breast cancer lymph node metastasis. *Cancer Res* (2007) 67(21):10582–91. doi: 10.1158/0008-5472.CAN-07-1655

3. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* (2013) 381(9869):805–16. doi: 10.1016/S0140-6736(12)61963-1

4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* (2005) 365(9472):1687–717. doi: 10.1016/S0140-6736(05)66544-0

5. Gradishar WJ, Anderson BO, Abraham J, Aft R, Agnese D, Allison KH, et al. Breast cancer, version 3.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw* (2020) 18(4):452–78. doi: 10.6004/jnccn.2020.0016

6. Dorjgochoo T, Gu K, Kallianpur A, Zheng Y, Zheng W, Chen Z, et al. Menopausal symptoms among breast cancer patients 6 months after diagnosis: a report from the shanghai breast cancer survival study. *Menopause* (2009) 16 (6):1205–12. doi: 10.1097/gme.0b013e3181aac32b

7. Zhu Y, Cohen SM, Rosenzweig MQ, Bender CM. Symptom map of endocrine therapy for breast cancer: a scoping review. *Cancer Nurs* (2019) 42(5):E19–30. doi: 10.1097/NCC.0000000000000632

8. Garreau JR, DeLaMelena T, Walts D, Karamlou K, Johnson N. Side effects of aromatase inhibitors versus tamoxifen: the patients' perspective. *Am J Surg* (2006) 192(4):496–8. doi: 10.1016/j.amjsurg.2006.06.018

9. Boehm DU, Lebrecht A, Eckhardt T, Albrich S, Schmidt M, Siggelkow W, et al. Quality of life and adjuvant tamoxifen treatment in breast cancer patients. *Eur J Cancer Care* (2009) 18(5):500–6. doi: 10.1111/j.1365-2354.2008.01015.x

10. Moon Z, Hunter MS, Moss-Morris R, Hughes LD. Factors related to the experience of menopausal symptoms in women prescribed tamoxifen. *J Psychosom Obstet Gynecol* (2017) 38(3):226–35. doi: 10.1080/0167482X.2016.1216963

11. Kim Y, Min YH. Menopausal symptoms and associated factors in breast cancer patients receiving hormone therapy. *J Korean Clin Nurs Res* (2017) 23 (1):120–9. doi: 10.22650/JKCNR.2017.23.1.120

12. Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. *Breast Cancer Res Treat* (2012) 134(1573-7217(1573-7217 (Electronic):459–78. doi: 10.1007/s10549-012-2114-5

13. Biglia N, Bounous VE, De Seta F, Lello S, Nappi RE, Paoletti AM. Non-hormonal strategies for managing menopausal symptoms in cancer survivors: an update. *Ecancermedicalscience* (2019) 13:909. doi: 10.3332/ecancer.2019.909

14. Cho MJ, Kim KH. Diagnostic validity of the CES-d (Korean version) in the assessment of DSM-III-R major depression. *J Korean Neuropsychiatr Assoc* (1993) 32(3):381–99.

15. Lintermans A, Van Asten K, Wildiers H, Laenen A, Paridaens R, Weltens C, et al. A prospective assessment of musculoskeletal toxicity and loss of grip strength in breast cancer patients receiving adjuvant aromatase inhibitors and tamoxifen, and relation with BMI. *Breast Cancer Res Treat* (2014) 146(1):109–16. doi: 10.1007/s10549-014-2986-7

16. Ochayon L, Tunin R, Yoselis A, Kadmon I. Symptoms of hormonal therapy and social support: is there a connection? comparison of symptom severity, symptom interference and social support among breast cancer patients receiving and not receiving adjuvant hormonal treatment. *Eur J Oncol Nurs* (2015) 19 (3):260–7. doi: 10.1016/j.ejon.2014.11.003

17. Rosenberg SM, Stanton AL, Petrie KJ, Partridge AH. Symptoms and symptom attribution among women on endocrine therapy for breast cancer. *Oncologist* (2015) 20(6):598. doi: 10.1634/theoncologist.2015-0007

18. Zhan M, Flaws JA, Gallicchio L, Tkaczuk K, Lewis LM, Royak-Schaler R. Profiles of tamoxifen-related side effects by race and smoking status in women with breast cancer. *Cancer Detect Prev* (2007) 31(5):384–90. doi: 10.1016/j.cdp.2007.10.004

19. Baxter SD, Teft WA, Choi Y-H, Winquist E, Kim RB. Tamoxifen-associated hot flash severity is inversely correlated with endoxifen concentration and CYP3A4* 22. *Breast Cancer Res Treat* (2014) 145(2):419–28. doi: 10.1007/s10549-014-2963-1

20. Jones SE, Cantrell J, Vukelja S, Pippen J, O'Shaughnessy J, Blum JL, et al. Comparison of menopausal symptoms during the first year of adjuvant therapy with either exemestane or tamoxifen in early breast cancer: report of a tamoxifen exemestane adjuvant multicenter trial substudy. *J Clin Oncol* (2007) 25(30):4765–71. doi: 10.1200/JCO.2007.10.8274

21. Shim EJ, Jeong D, Lee SB, Min YH. Trajectory of fear of cancer recurrence and beliefs and rates of medication adherence in patients with breast cancer. *Psychooncology* (2020) 29(11):1835–41. doi: 10.1002/pon.5497

22. Heinemann K, Ruebig A, Potthoff P, Schneider HPG, Strelow F, Heinemann LAJ, et al. The menopause rating scale (MRS) scale: a methodological review. *Health Qual Life Outcomes* (2004) 2(45). doi: 10.1186/1477-7525-2-45

23. Moon Z, Moss-Morris R, Hunter MS, Norton S, Hughes LD. Nonadherence to tamoxifen in breast cancer survivors: A 12 month longitudinal analysis. *Health Psychol* (2019) 38(10):888. doi: 10.1037/hea0000785

24. Hunter MS, Grunfeld EA, Mittal S, Sikka P, Ramirez AJ, Fentiman I, et al. Menopausal symptoms in women with breast cancer: prevalence and treatment preferences. *Psychooncology* (2004) 13(11):769–78. doi: 10.1002/pon.793

25. Gupta P, Sturdee D, Palin S, Majumder K, Fear R, Marshall T, et al. Menopausal symptoms in women treated for breast cancer: the prevalence and severity of symptoms and their perceived effects on quality of life. *Climacteric* (2006) 9(1):49–58. doi: 10.1080/13697130500487224

26. Brett J, Fenlon D, Boulton M, Hulbert-Williams NJ, Walter FM, Donnelly P, et al. Factors associated with intentional and unintentional non-adherence to adjuvant endocrine therapy following breast cancer. *Eur J Cancer Care* (2018) 27 (1):e12601. doi: 10.1111/ecc.12601

27. Saibil S, Fitzgerald B, Freedman O, Amir E, Napolskikh J, Salvo N, et al. Incidence of taxane-induced pain and distress in patients receiving chemotherapy for early-stage breast cancer: a retrospective, outcomes-based survey. *Curr Oncol* (2010) 17(4):42–7. doi: 10.3747/co.v17i4.562

28. Jones SE, Savin MA, Holmes FA, O'Shaugnessy JA, Blum JL, Vukelja S, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol* (2006) 24(34):5381–7. doi: 10.1200/JCO.2006.06.5391

29. Fenlon D, Addington-Hall JM, O'Callaghan AC, Clough J, Nicholls P, Simmonds P. A survey of joint and muscle aches, pain, and stiffness comparing women with and without breast cancer. *J Pain Symptom Manage* (2013) 46(4):523–35. doi: 10.1016/j.jpainsymman.2012.10.282

30. Miaskowski C. Gender differences in pain, fatigue, and depression in patients with cancer. *JNCI Monographs* (2004) 2004(32):139–43. doi: 10.1093/jncimonographs/lgh024

31. Green CR, Hart-Johnson T, Loeffler DR. Cancer-related chronic pain: examining quality of life in diverse cancer survivors. *Cancer* (2011) 117(9):1994–2003. doi: 10.1002/cncr.25761

32. Knobf MT, Sun Y. A longitudinal study of symptoms and self-care activities in women treated with primary radiotherapy for breast cancer. *Cancer Nurs* (2005) 28(3):210–8. doi: 10.1097/00002820-200505000-00010

33. Sanford SD, Wagner LI, Beaumont JL, Butt Z, Sweet JJ, Cella D. Longitudinal prospective assessment of sleep quality: before, during, and after adjuvant chemotherapy for breast cancer. *Support Care Cancer* (2013) 21(4):959–67. doi: 10.1007/s00520-012-1612-7

34. De Jong N, Candel M, Schouten H, Abu-Saad HH, Courtens A. Prevalence and course of fatigue in breast cancer patients receiving adjuvant chemotherapy. *Ann Oncol* (2004) 15(6):896–905. doi: 10.1093/annonc/mdh229

35. Nho JH, Kim SR, Park MH, Kweon SS. Symptom clusters and quality of life in breast cancer survivors after cancer treatment in a tertiary hospital in Korea. *Eur J Cancer Care* (2018) 27(6):e12919. doi: 10.1111/ecc.12919

36. Bjerkeset E, Röhrl K, Schou-Bredal I. Symptom cluster of pain, fatigue, and psychological distress in breast cancer survivors: prevalence and characteristics. *Breast Cancer Res Treat* (2020) 180(1):63–71. doi: 10.1007/s10549-020-05522-8

37. Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep* (2004) 27 (7):1255–73. doi: 10.1093/sleep/27.7.1255

38. Vitiello MV, Larsen LH, Moe KE. Age-related sleep change: gender and estrogen effects on the subjective–objective sleep quality relationships of healthy, noncomplaining older men and women. *J Psychosom Res* (2004) 56(5):503–10. doi: 10.1016/S0022-3999(04)00023-6

39. Cimprich B, Ronis DL, Martinez-Ramos G. Age at diagnosis and quality of life in breast cancer survivors. *Cancer Pract* (2002) 10(2):85–93. doi: 10.1046/j.1523-5394.2002.102006.x

40. Grunfeld EA, Hunter MS, Sikka P, Mittal S. Adherence beliefs among breast cancer patients taking tamoxifen. *Patient Educ Couns* (2005) 59(1):97–102. doi: 10.1016/j.pec.2004.10.005

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 05 August 2022
DOI 10.3389/fonc.2022.807531



OPEN ACCESS

EDITED BY
Julio de la Torre,
Comillas Pontifical University, Spain

REVIEWED BY
Laura Cortesi,
University Hospital of Modena, Italy
Marco Invernizzi,
University of Eastern Piedmont, Italy

*CORRESPONDENCE
Xiaohui Hou
houxh@gzsport.edu.cn
Min Hu
whoomin@hotmail.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

RECEIVED 02 November 2021
ACCEPTED 01 July 2022
PUBLISHED 05 August 2022

CITATION
Liao J, Chen Y, Cai L, Wang K, Wu S, Wu L, Song B, Hu M and Hou X (2022) Baduanjin's impact on quality of life and sleep quality in breast cancer survivors receiving aromatase inhibitor therapy: A randomized controlled trial. *Front. Oncol.* 12:807531. doi: 10.3389/fonc.2022.807531



# Baduanjin's impact on quality of life and sleep quality in breast cancer survivors receiving aromatase inhibitor therapy: a randomized controlled trial

Jingwen Liao[1,2†], Yanyu Chen[3†], Li Cai[4], Kun Wang[5], Shenghui Wu[6], Lan Wu[4], Bixiao Song[3], Min Hu[1*] and Xiaohui Hou[3,7,8*]

[1]Guangdong Provincial Key Laboratory of Physical Activity and Health Promotion, Guangzhou Sport University, Guangzhou, China, [2]Scientific Research Center, Guangzhou Sport University, Guangzhou, China, [3]Department of Sports and Health, Guangzhou Sport University, Guangzhou, China, [4]Department of Martial Arts, Guangzhou Sport University, Guangzhou, China, [5]Department of Breast Cancer, Cancer Center, Guangdong Provincial People's General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China, [6]Department of Epidemiology and Biostatistics, University of Texas Health San Antonio, Laredo, TX, United States, [7]School of Kinesiology, Shanghai University of Sport, Shanghai, China, [8]The Sports and Health Promotion International Collaboration and Innovation Center for People with Disability, Guangzhou, China

**Purpose:** The aim of the current study is to investigate the impact of Baduanjin, a traditional Chinese exercise, on quality of life and sleep quality in breast cancer survivors receiving aromatase inhibitor (AI) therapy.

**Methods:** A total of 72 breast cancer survivors who had received AI treatment for more3 than 6 months were enrolled in the current study using non-probability consecutive sampling procedure. Participants were randomly assigned in a 1:1 ratio to a 12-week Baduanjin exercise program or to a wait-list control group. The Baduanjin exercise group performed two 90-min supervised sessions per week. The primary outcomes were changes in quality of life measured by the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30) and in sleep quality evaluated using the Pittsburgh Sleep Quality Index (PSQI).

**Results:** A total of 68 participants completed the trial (Baduanjin exercise group: n = 33; control group: n = 35). Baseline values for quality of life did not differ between groups. Both global quality of life and physical functioning scores increased significantly by 12.39 ($P < 0.001$) and 8.48 ($P < 0.001$) in the Baduanjin exercise group compared with those in the control. Overall PSQI score also decreased by 4.85 ($P < 0.001$) in the Baduanjin exercise group, whereas it increased by 0.34 in the control group.

**Conclusion:** Baduanjin exercise training led to improvement in the quality of life and sleep quality of breast cancer patients undergoing AI therapy.

KEYWORDS

breast cancer survivors, quality of life, sleep quality, aromatase inhibitor therapy, Baduanjin exercise

# Introduction

Breast cancer is the most diagnosed neoplasm and the most represented cause of death in women worldwide (1). Aromatase inhibitors (AIs), a form of endocrine therapy, are a mainstay of the adjuvant approach for reducing the growth-stimulatory effects of estrogen in hormone-positive breast cancer of postmenopausal women (2). However, AIs would cause side effects including myalgia, arthralgia, and fatigue that may lead to medication non-adherence and significant decrease in quality of life (3, 4). Furthermore, there is evidence in the literature that approximately 20%–70% of breast cancer patients suffer from poor sleep quality (5). Due to these adverse impacts, adherence to AI therapy is poor (6, 7). Furthermore, long-term cancer treatment imposes an economic burden on cancer patients and subsequently reduces their quality of life (8, 9). Therefore, it is important to develop effective and affordable treatment strategies to improve quality of life and sleep quality for breast cancer patients undergoing AI therapy.

The effectiveness of exercise interventions on alleviating the negative effects of treatments in breast cancer patients and survivors has been well reviewed (10). More recent evidence supports that both resistant exercise (11) and mixed protocols (including sessions of aerobic and strength training) (12, 13) are safe and effective in muscle function, physical performance, and quality of life among breast cancer patients with AI treatment. An interesting type of physical exercise (compared to established types such as aerobic exercise) that might be beneficial for breast cancer patients is Baduanjin (14), a traditional Chinese mind–body exercise incorporating and combining different slow-motions and breathing exercises (15). One advantage of Baduanjin is that it is based on eight simple movements that can be easily learned and are derived from Chinese medical theory (16). On the other hand, Baduanjin has been reported to be safe to perform with relatively few adverse events (17). The beneficial effects of Baduanjin have been fully reviewed; it can improve cognitive function (15, 18), cardiopulmonary function (19), and mental illness (20). Even though there are studies reporting that the Baduanjin exercise had positive clinical effects on breast cancer patients (including quality of life and sleep quality) (21, 22), few indicated the use of AIs. It is currently not well-investigated whether the Baduanjin exercise is an effective way to improve self-reported quality of life and sleep quality in breast cancer survivors undergoing AI treatment. Thus, the aim of the current study is to examine the impact of Baduanjin on measures of self-reported quality of life and sleep quality in breast cancer patients undergoing AI therapy.

# Materials and methods

## Study design and recruitment

This single-blinded randomized controlled trial was conducted in Guangdong Provincial People's Hospital at baseline and 12 weeks after the treatment using consecutive sampling. This non-probability sample selection for the recruitment is a rigorous process of conducting research including those who meet the predefined inclusion and exclusion requirements by the residents. Therefore, every breast cancer survivor staying in the hospital had an equal chance of being recruited as a participant in this study. Eligible participants met the following criteria: 1) age between 18 and 75 years; 2) diagnosis with stage I–III breast cancer for 6 months to 8 years prior to recruitment; 3) undergoing AI treatment for more than 6 months; and 4) never participated in Baduanjin exercise training in the last 6 months or no previous Baduanjin training experience for more than 3 months. The following exclusion criteria were used: 1) unstable or serious neurologic disease, musculoskeletal disorder, renal failure, cardiovascular or respiratory diseases such as uncontrolled hypertension, and chronic obstructive pulmonary disease; 2) plan of a surgery, such as a joint replacement for the next 6 months; or 3) high-intensity physical exercise experience more than 5 h per week. The ethics committee of Guangdong Provincial People's General Hospital [Approval No. GDREC2016424H (R1)] approved this research protocol, and each participant has provided written informed consent. This trial was registered in ClinicalTrials.gov PRS (NCT03162133), and all procedures were in accordance with the principles stated in the Declaration of Helsinki.

## Baduanjin intervention

Eligible participants were allocated either to a 12-week Baduanjin intervention group or to a wait-list control group (Figure 1). After baseline tests, participants of the Baduanjin intervention group were instructed to attend a Baduanjin program. The program was composed of 90 min per session with 2 sessions per week (Monday and Wednesday) for 12 weeks. Each session consisted of a 10-min warm-up, a 70-min Baduanjin form,

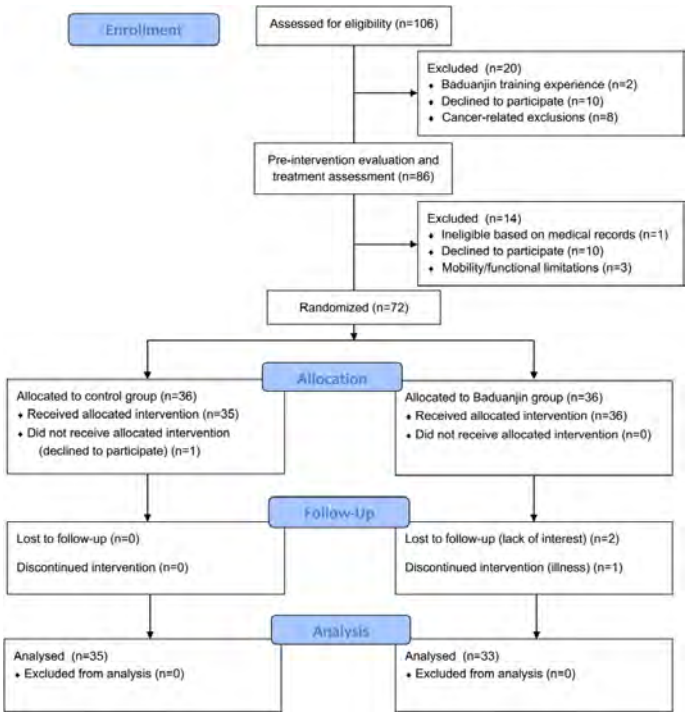



FIGURE 1
Flow Diagram Depicting the Study Design

and a 10-min cooldown. The whole Baduanjin form included eight postures and was in accordance with the standardized Baduanjin training program "Health Qigong Baduanjin Standard" established by the General Administration of Sports of China (23). Briefly, the 8 postures were (as shown in Figure 2): 1) prop both hands to the sky; 2) draw a bow on both sides like shooting a vulture; 3) raise a single arm; 4) look back; 5) sway the head and shake the tail; 6) clench fists; 7) touch toes by hands with flexion of hip and extension of knee joint; 8) rise and bounce on the toes seven times. Two senior Baduanjin instructors from Guangzhou Sports University conducted the training and recorded the participants' attendance. Participants of the wait-list control group were instructed to continue performing their usual care and daily activities and to refrain from doing any Baduanjin exercise. After their posttest, they were able to attend the Baduanjin program.

## Outcome measurements

### Quality of life: European organization for research and treatment of cancer quality-of-life questionnaire core 30

The primary outcome was quality of life measured by European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30), which is a 30-item scale that are grouped into the following: five function scales (physical, role, emotional, cognitive, and social), nine symptom scales (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global score of quality of life. All scales were linearly transformed to a 0–100 score according to the EORTC Scoring Manual. A higher score for functional scales and global quality of life reflects a better level of functioning, while a higher score in symptom scales indicates a high level of problems (24).

### Sleep quality: Pittsburgh sleep quality index

The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality at baseline an d post-intervention. The questionnaire consists of 19 questions, and seven component scores were then generated: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Scoring of answer was based on a scale of 0–3 (total score of 21). A global score was calculated from summing the subscale scores. Lower scores indicate better sleep quality.

FIGURE 2
Eight Postures of the Baduanjin Form.

## Demographics and medical history

Demographic data (name, age, weight, height, marital status, and employment status) were collected by interviewing the participants. Medical history (time since diagnosis, time since initiating AI, breast cancer stage, type of surgery, comorbidities, and complications) was obtained from medical records.

## Sample size

The population of the current study included individuals diagnosed with breast cancer. In order to calculate the sample size, power was assumed as 0.90 and type 1 error as 0.05. Considering a 20% attrition rate, a sample size of 72 participants for the two groups was finally decided to be needed. Power in changes of quality of life (EORTC QLQ-C30) was calculated to determine the effect size (d) of the Baduanjin intervention. Power in global quality of life was 0.999 (d = 0.704); the highest power was found in Physical functioning by 0.999 (d = 0.746) and lowest in Financial by 0.055 (d = 0.005). Effect size is interpreted as d = 0.20 (small), d = 0.50 (medium), and d = 0.80 (large).

## Randomization and blinding

After baseline assessment, 72 patients who met the inclusion and exclusion criteria were allocated by simple randomization with 1:1 ratio (control group:exercise group) performed by the random number table. Allocation concealment was conducted by the envelope method. Due to the obviously different programs between groups, this study is a single-blinded study. The outcome measurements were evaluated by trained assessors who were unaware of group allocation; the participant was required not to talk about the received intervention.

## Statistical analyses

SPSS 17.0 (IBM, Armonk, NY, USA) was used to perform all statistical tests. Descriptive analyses were applied to characterize baseline patients; differences between groups were compared using independent-samples t-test for continuous data and chi-square test for categorical data. The primary outcomes (scores of the EORTC QLQ-C30 or PSQI) between groups of baseline, post-intervention, or the changes used independent-samples t-test. Intragroup differences were analyzed using paired t-test. Analysis of the outcomes was performed based on the intention-to-treat principle. Minimal detectable change at 90% confidence ($MDC_{90}$) was calculated to evaluate the efficacy of the Baduanjin training on outcome measures. The level of significance was set for all statistical tests at $P < 0.05$.

# Results

## Flow of participants through the trial and baseline characteristics

Participants were recruited from the Breast Surgery Clinic of Guangdong Provincial People's General Hospital from November 2016 to May 2017 using a non-probability consecutive sampling. Among the 72 patients who met the enrollment criteria and were willing to participate, 38 participants completed the trials and were included in the analysis. Figure 1 shows the flow of participants throughout the trial. Table 1 presents the baseline characteristics.

TABLE 1 Baseline characteristics of patients*.

| Characteristics | Control group (n = 35) | Exercise group (n = 33) | P# |
|---|---|---|---|
| Age, years | 54.63 (8.44) | 53.12 (7.02) | 0.905 |
| BMI, kg/m$^2$ | 23.37 (3.92) | 22.14 (2.67) | 0.450 |
| Marital status, No. (%) | | | |
| Married | 31 (88.6) | 22 (66.7) | 0.058 |
| Divorced/separated | 1 (2.9) | 0 (0) | |
| Single | 0 (0) | 2 (6.1) | |
| Unclear | 3 (8.6) | 9 (27.3) | |
| Employment status, No. (%) | | | |
| Employed full- or part-time | 16 (45.7) | 14 (42.4) | 0.530 |
| Unemployed | 3 (8.6) | 3 (9.1) | |
| Retired | 14 (40.0) | 16 (48.5) | |
| Unclear | 2 (5.7) | 0 (0) | |
| Time since diagnosis, years | 2.17 (2.13) | 3.00 (2.54) | 0.244 |
| Time since initiating AI, years | 6.66 (2.27) | 2.40 (2.31) | 0.195 |
| Overall grade, No. (%) | | | |
| I | 10 (28.6) | 5 (15.2) | 0.548 |
| II | 16 (45.7) | 20 (60.6) | |
| III | 8 (22.9) | 7 (21.2) | |
| Missing/NA | 1 (2.9) | 1 (0) | |

BMI, body mass index; SD, standard deviation; AI, aromatase inhibitor.
*Data are presented as the mean (SD) for continuous variables and frequency (percentage) for categorical variables.
#P value for difference between groups.

## Outcomes and estimation

### Changes in quality of life

Table 2 summarizes the quality of life outcomes based on scores of the EORTC QLQ-C30. The baseline scores did not differ between the two groups. After 12 weeks of intervention, significant changes from baseline were observed for most functional scales, some symptom scales, and global score ($P < 0.05$). Functional scales increased significantly, among which physical functioning score increased by 8.48 in the exercise group while it decreased by 3.66 in the control ($P < 0.01$). For symptom scales, significant decreases in the Baduanjin exercise group were also observed for fatigue ($P = 0.010$), nausea/vomiting ($P = 0.047$), pain ($P = 0.014$), insomnia ($P = 0.020$), and diarrhea ($P = 0.038$) compared with those in the control.

### Changes in sleep quality

Table 3 summarizes the sleep quality index based on scores of the PSQI. The baseline values for sleep quality did not differ between groups. Overall change of PSQI score decreased by 4.85 in the Baduanjin exercise group compared with 0.34 in the control group ($P < 0.01$). Significant changes from baseline to post-intervention were also observed for sleep quality ($P = 0.001$), sleep latency ($P = 0.007$), sleep duration ($P = 0.010$), sleep efficiency ($P = 0.001$), sleep disturbances ($P = 0.001$), and daytime dysfunction ($P = 0.001$). Results of the $MDC_{90}$ estimates and the proportion of participants who met the $MDC_{90}$ were summarized in Supplementary Table S1.

## Adverse events

Thirty-three (92%) of the 36 total participants in the Baduanjin exercise group completed the training sessions. There were no major adverse events or complications found during the study.

# Discussion

The objective of this study was to evaluate the effectiveness of the Baduanjin exercise employed in breast cancer patients who were under AI treatment. The data suggest that 12-week Baduanjin exercise significantly increases self-reported quality of life and sleep quality in those participants when compared with those in the control group. In the intragroup analysis, there were significant statistical differences only in the Baduanjin intervention group. Results from this study support the hypothesis that Baduanjin has positive influences on most functioning subscales and global score of quality of life; sleep quality scores were also beneficially changed. AI treatment in breast cancer patients has several serious side effects such as musculoskeletal problems (25), menopausal syndromes (26),

TABLE 2 Effects of Baduanjin on quality of life (EORTC QLQ-C30)*.

| | Baseline | | P# | Post-intervention | | P# | Change | | P& |
|---|---|---|---|---|---|---|---|---|---|
| | Control | Exercise | | Control | Exercise | | Control | Exercise | |
| Physical functioning | 85.31 ± 14.84 | 82.91 ± 12.03 | 0.261 | 81.66 ± 13.35 | 91.39 ± 7.58 | 0.513 | -3.66 ± 13.78 | 8.48 ± 8.65 | 0.000 |
| Role functioning | 89.97 ± 16.77 | 85.45 ± 18.98 | 0.251 | 88.69 ± 16.49 | 92.33 ± 10.81 | 0.869 | -1.29 ± 14.64 | 6.88 ± 17.66 | 0.015 |
| Emotional functioning | 78.29 ± 13.95 | 75.52 ± 18.72 | 0.700 | 78.06 ± 13.45 | 84.94 ± 13.39 | 0.330 | -0.23 ± 12.36 | 9.42 ± 19.15 | 0.010 |
| Cognitive functioning | 79.91 ± 17.94 | 75.64 ± 20.8 | 0.440 | 79.09 ± 15.80 | 84.85 ± 10.79 | 0.882 | -0.83 ± 17.00 | 9.21 ± 21.42 | 0.026 |
| Social functioning | 82.37 ± 20.57 | 78.21 ± 29.03 | 0.834 | 84.8 ± 18.61 | 87.73 ± 17.61 | 0.121 | 2.43 ± 18.29 | 9.52 ± 24.72 | 0.193 |
| Fatigue | 32.23 ± 23.61 | 31.12 ± 19.88 | 0.789 | 27.49 ± 22.16 | 14.24 ± 12.47 | 0.855 | -4.74 ± 19.98 | -16.88 ± 19.75 | 0.010 |
| Nausea/vomiting | 0.97 ± 4.00 | 4.61 ± 12.79 | 0.109 | 0.94 ± 5.58 | 0.52 ± 2.96 | 0.932 | -0.03 ± 4.00 | -4.09 ± 12.62 | 0.047 |
| Pain | 29.51 ± 23.17 | 28.36 ± 22.58 | 0.781 | 23.37 ± 21.46 | 12.67 ± 13.12 | 0.851 | -6.14 ± 18.52 | -15.70 ± 14.45 | 0.014 |
| Dyspnea | 12.29 ± 18.14 | 14.06 ± 20.42 | 0.792 | 10.4 ± 17.58 | 10.06 ± 17.09 | 0.272 | -1.89 ± 19.61 | -4.00 ± 21.98 | 0.633 |
| Insomnia | 32.26 ± 29.73 | 30.21 ± 33.73 | 0.576 | 33.26 ± 29.23 | 15.64 ± 20.73 | 0.486 | 1.00 ± 24.96 | -14.58 ± 30.36 | 0.020 |
| Appetite loss | 3.77 ± 10.65 | 8.03 ± 16.67 | 0.261 | 4.71 ± 11.72 | 3.55 ± 9.07 | 0.827 | 0.94 ± 12.62 | -4.48 ± 17.77 | 0.251 |
| Constipation | 8.51 ± 16.78 | 11.06 ± 23.04 | 0.836 | 7.54 ± 14.06 | 1.00 ± 5.74 | 0.400 | -0.97 ± 15.01 | -10.06 ± 22.77 | 0.092 |
| Diarrhea | 2.83 ± 9.37 | 7.00 ± 13.70 | 0.144 | 6.60 ± 13.39 | 4.00 ± 10.94 | 0.827 | 3.77 ± 10.65 | -3.00 ± 15.13 | 0.038 |
| Financial | 18.00 ± 24.68 | 21.18 ± 31.01 | 0.939 | 15.14 ± 20.31 | 18.15 ± 32.38 | 0.523 | -2.86 ± 20.39 | -3.03 ± 24.07 | 0.810 |
| Global quality of life | 71.94 ± 19.47 | 67.15 ± 11.22 | 0.319 | 69.63 ± 17.14 | 79.55 ± 10.58 | 0.627 | -2.31 ± 19.25 | 12.39 ± 8.08 | 0.000 |

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; SD, standard deviation.
*Data were presented as mean ± SD; control group (n = 35); exercise group (n = 33).
#P value for difference between groups at baseline or post-intervention.
&P value for change between groups from baseline to post-intervention.

and sleep disorders (27), which can lead to low treatment adherence (6) and reduced quality of life (7). It has been consistently shown that the Baduanjin exercise can improve breast cancer patients' quality of life and sleep quality (22); however, to the best of our knowledge, there are few randomized clinical trials available that evaluated the effect of the Baduanjin training in breast cancer patients under AI treatment.

Several instruments identifying quality of life have been validated for breast cancer survivors, among which the EORTC QLQ-C30 and Functional Assessment of Cancer Therapy-Breast (FACT-B) are most commonly used for the Baduanjin intervention on breast cancer patients (4). The current results of quality of life based on the EORTC QLQ-C30 showed that Baduanjin had obvious beneficial effects on most functioning subscales (physical, role, emotional, and cognitive functioning); in particular, the change of physical functioning in the intervention group increased by 8.48 while it decreased by 3.66 in the control group with significant difference. Notably, the change in fatigue symptom subscales in the Baduanjin group was also significantly lower than that of the control, and the global quality of life score increased by 12.39 compared with 2.31 decrease in the control group. These results reached or exceeded the minimal important difference established in a previous study with patients suffering from

TABLE 3 Effects of Baduanjin on sleep quality index (PSQI)*.

| | Baseline | | P# | Post-intervention | | P# | Change | | P& |
|---|---|---|---|---|---|---|---|---|---|
| | Control | Exercise | | Control | Exercise | | Control | Exercise | |
| Subjective sleep quality | 1.57 ± 0.81 | 1.73 ± 0.84 | 0.455 | 1.49 ± 0.89 | 0.91 ± 0.63 | 0.769 | -0.09 ± 0.85 | -0.82 ± 0.77 | 0.001 |
| Sleep latency | 1.66 ± 1.11 | 1.67 ± 1.14 | 0.965 | 1.57 ± 1.12 | 1.00 ± 0.71 | 0.913 | -0.09 ± 0.74 | -0.67 ± 0.89 | 0.007 |
| Sleep duration | 1.57 ± 0.85 | 1.61 ± 0.90 | 0.870 | 1.51 ± 0.95 | 1.06 ± 0.70 | 0.384 | -0.06 ± 0.68 | -0.55 ± 0.71 | 0.010 |
| Sleep efficiency | 1.06 ± 1.08 | 1.15 ± 1.20 | 0.897 | 1.29 ± 1.25 | 0.39 ± 0.56 | 0.066 | 0.23 ± 1.00 | -0.76 ± 1.06 | 0.001 |
| Sleep disturbances | 1.49 ± 0.61 | 1.64 ± 0.86 | 0.508 | 1.43 ± 0.70 | 0.82 ± 0.58 | 0.648 | -0.06 ± 0.68 | -0.82 ± 0.95 | 0.001 |
| Use of sleeping medication | 0.40 ± 0.77 | 0.33 ± 0.85 | 0.375 | 0.31 ± 0.76 | 0.15 ± 0.44 | 0.361 | -0.09 ± 0.70 | -0.18 ± 0.68 | 0.566 |
| Daytime dysfunction | 1.89 ± 0.99 | 2.00 ± 1.00 | 0.607 | 1.69 ± 0.99 | 0.94 ± 0.50 | 0.657 | -0.20 ± 0.99 | -1.06 ± 0.93 | 0.001 |
| PSQI score | 9.63 ± 3.98 | 10.12 ± 4.05 | 0.615 | 9.29 ± 4.52 | 5.27 ± 2.14 | 0.401 | -0.34 ± 2.73 | -4.85 ± 2.96 | 0.000 |

PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation.
*Data were presented as mean ± SD; control group (n = 35); exercise group (n = 33).
#P value for difference between groups at baseline or post-intervention.
&P value for change between groups from baseline to post-intervention.

advanced cancer (28). Since fatigue is one of the most disturbing adverse reactions in breast cancer patients and can seriously affect the patient's physical function and quality of life (29, 30), the Baduanjin training-induced decrease of fatigue scores might be one important factor contributing to the improved self-reported quality of life (31). The current observation is in line with recent published studies (14, 18) that focus on the influences of the Baduanjin intervention on physical and psychological health and cognitive function among in women with breast cancer even receiving chemotherapy.

Sleep-related disorders such as insomnia complaints exceed half of AI users who were diagnosed with breast cancer, which is also highly associated with other clinical symptoms including anxiety, depression, and hot flashes (27). In the current study, we observed that the Baduanjin training improved self-reported sleep quality (indicated by lower PSQI scores except for the use of sleeping medication); previous studies also found that Baduanjin significantly improved insomnia measured by PSQI with elevated levels of serum melatonin (32). For breast cancer patients under AI therapy, our findings address the gap and additionally support that the Baduanjin training is an effective intervention strategy leading to improvement of self-reported quality of life.

Even though the biological process contributing to the observed outcome is unclear, inflammatory markers might play a role. Chronic inflammation is present in breast cancer (33) and is considered as a key biological factor causing fatigue and decreased physical function in those patients (34). There is evidence that among women taking AIs, the coexistence of fatigue, insomnia, and arthralgia shared an inflammaotry mechanism (35) and that mind–body interventions (such as Baduanjin) could reduce inflammatory markers (36). Hence, it seems reasonable to speculate that long-term Baduanjin training might suppress inflammatory activities caused by AI treatment; to prove this assumption, further well-designed research is required. Moreover, studies focusing on this effectiveness of the Baduanjin training were encouraged to include physical performance (muscle strength) and physiological parameters (heart rate variability and body composition) as objective measurements, which would add to the evidence derived from questionnaires.

Given that the Baduanjin training is a safe, low-cost, and whole-body intervention that requires the use of multiple muscles and joints and incorporated rhythmic abdominal breathing and meditation (19), our findings support the idea that the Baduanjin training can be an effective intervention strategy in breast cancer patients undergoing AI treatment.

This study has 2 limitations. Firstly, inhibitor-induced arthralgia symptoms were not included as part of the evaluation because not all patients had inhibitor-induced arthralgia, which might lead to underestimation of Baduanjin's potential benefit. Secondly, we did not collect lifestyle data on the level of physical activity in both groups; it is unclear whether patients were participating in other types of low- to moderate-intensity exercise during the intervention.

## Conclusion

In summary, the current study suggests that 12-week Baduanjin exercise training may be a low-risk, well-tolerated, and safe intervention strategy that leads to improvements of self-reported quality of life and subjective sleep quality in breast cancer patients undergoing AI treatment.

## Data availability statement

The raw data supporting the conclusion of this current study will made available by the corresponding authors without undue reservation.

## Ethics statement

This study involving human participants were reviewed and approved by the Ethics Committee of Guangdong Provincial People's General Hospital. All participants provided written informed consent. This trial was registered in Clinical Trials.gov and all procedures were in accordance with the principles stated in the declaration of Helsinki.

## Author contributions

JL analyzed the data, drew the graph, and drafted the tables and manuscript. YC conceived and designed the research, performed the research, analyzed the data, contributed to materials and analysis tools. LC performed the research and conduct the Badaunjin exercise program. KW, SW, LW, and BS contributed to conceiving the trial, performing the research, and analyzing the data. MH and XH designed the research, provided assistance, and reviewed the manuscript and tables. All authors contributed to the article and approved the submitted version.

## Funding

This study was supported by grants from the collaborative innovation team of physical activity and health promotion for the Great Bay Area of Guangdong-HongKong-Macau, the Major Science and Technology Projects of Guangdong Province (No. 20130325C), Distinguishing Innovation Project of Department of Education of Guangdong Province (No. 2015 KTSCX080; No. 2016KTSCX070), and the Major International Cooperation

Project of Department of Education of Guangdong Province (No. 2014WGJHZ005).

## Acknowledgments

The authors would like to thank Lina Zhao, School of Public Health, Sun Yat-sen University for her assistance with reviewing drafts of the paper.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.807531/full#supplementary-material

## References

1. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, et al. Breast cancer statistics, 2019. *CA Cancer J Clin* (2019) 69(6):438–51. doi: 10.3322/caac.21583

2. Burstein HJ, Lacchetti C, Griggs JJ. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. *J Oncol Pract* (2019) 15(2):106–7. doi: 10.1200/JOP.18.00617

3. Laroche F, Perrot S, Medkour T, Cottu PH, Pierga JY, Lotz JP, et al. Quality of life and impact of pain in women treated with aromatase inhibitors for breast cancer. a multicenter cohort study. *PloS One* (2017) 12(11):e0187165. doi: 10.1371/journal.pone.0187165

4. Chopra I, Kamal KM. A systematic review of quality of life instruments in long-term breast cancer survivors. *Health Qual Life Outcomes* (2012) 10:14. doi: 10.1186/1477-7525-10-14

5. Fiorentino L, Ancoli-Israel S. Insomnia and its treatment in women with breast cancer. *Sleep Med Rev* (2006) 10(6):419–29. doi: 10.1016/j.smrv.2006.03.005

6. Verma S, Madarnas Y, Sehdev S, Martin G, Bajcar J. Patient adherence to aromatase inhibitor treatment in the adjuvant setting. *Curr Oncol* (2011) 18 Suppl 1:S3–9. doi: 10.3747/co.v18i0.899

7. Berkowitz MJ, Thompson CK, Zibecchi LT, Lee MK, Streja E, Berkowitz JS, et al. How patients experience endocrine therapy for breast cancer: an online survey of side effects, adherence, and medical team support. *J Cancer Surviv* (2021) 15 (1):29–39. doi: 10.1007/s11764-020-00908-5

8. Meneses K, Azuero A, Hassey L, McNees P, Pisu M. Does economic burden influence quality of life in breast cancer survivors? *Gynecol Oncol* (2012) 124 (3):437–43. doi: 10.1016/j.ygyno.2011.11.038

9. Barron JJ, Quimbo R, Nikam PT, Amonkar MM. Assessing the economic burden of breast cancer in a US managed care population. *Breast Cancer Res Treat* (2008) 109(2):367–77. doi: 10.1007/s10549-007-9650-4

10. Del-Rosal-Jurado A, Romero-Galisteo R, Trinidad-Fernandez M, Gonzalez-Sanchez M, Cuesta-Vargas A, Ruiz-Munoz M. Therapeutic physical exercise post-treatment in breast cancer: A systematic review of clinical practice guidelines. *J Clin Med* (2020) 9(4): 1239. doi: 10.3390/jcm9041239

11. Ramirez-Parada K, Lopez-Garzon M, Sanchez-Rojel C, Petric-Guajardo M, Alfaro-Barra M, Fernandez-Verdejo R, et al. Effect of supervised resistance training on arm volume, quality of life and physical perfomance among women at high risk for breast cancer-related lymphedema: A study protocol for a randomized controlled trial (STRONG-b). *Front Oncol* (2022) 12:850564. doi: 10.3389/fonc.2022.850564

12. Invernizzi M, de Sire A, Lippi L, Venetis K, Sajjadi E, Gimigliano F, et al. Impact of rehabilitation on breast cancer related fatigue: A pilot study. *Front Oncol* (2020) 10:556718. doi: 10.3389/fonc.2020.556718

13. de Sire A, Lippi L, Ammendolia A, Cisari C, Venetis K, Sajjadi E, et al. Physical exercise with or without whole-body vibration in breast cancer patients suffering from aromatase inhibitor-induced musculoskeletal symptoms: A pilot randomized clinical study. *J Pers Med* (2021) 11(12): 1369. doi: 10.3390/jpm11121369

14. Ying W, Min QW, Lei T, Na ZX, Li L, Jing L. The health effects of baduanjin exercise (a type of qigong exercise) in breast cancer survivors: A randomized, controlled, single-blinded trial. *Eur J Oncol Nurs* (2019) 39:90–7. doi: 10.1016/j.ejon.2019.01.007

15. Zou L, Pan Z, Yeung A, Talwar S, Wang C, Liu Y, et al. A review study on the beneficial effects of baduanjin. *J Altern Complement Med* (2018) 24(4):324–35. doi: 10.1089/acm.2017.0241

16. Koh TC. Baduanjin – an ancient Chinese exercise. *Am J Chin Med* (1982) 10 (1–4):14–21. doi: 10.1142/S0192415X8200004X

17. Fang J, Zhang L, Wu F, Ye J, Cai S, Lian X. The safety of baduanjin exercise: A systematic review. *Evid Based Complement Alternat Med* (2021) 2021:8867098. doi: 10.1155/2021/8867098

18. Wei XL, Yuan RZ, Jin YM, Li S, Wang MY, Jiang JT, et al. Effect of baduanjin exercise intervention on cognitive function and quality of life in women with breast cancer receiving chemotherapy: study protocol of a randomized controlled trial. *Trials* (2021) 22(1):405. doi: 10.1186/s13063-021-05355-w

19. Zou L, SasaKi JE, Wang H, Xiao Z, Fang Q, Zhang M. A systematic review and meta-analysis baduanjin qigong for health benefits: Randomized controlled trials. *Evid Based Complement Alternat Med* (2017) 2017:4548706. doi: 10.1155/2017/4548706

20. Zou L, Yeung A, Quan X, Hui SS, Hu X, Chan JSM, et al. Mindfulness-based baduanjin exercise for depression and anxiety in people with physical or mental illnesses: A systematic review and meta-analysis. *Int J Environ Res Public Health* (2018) 15(2): 321. doi: 10.3390/ijerph15020321

21. Meng T, Hu SF, Cheng YQ, Ye MN, Wang B, Wu JJ, et al. Qigong for women with breast cancer: An updated systematic review and meta-analysis. *Complement Ther Med* (2021) 60:102743. doi: 10.1016/j.ctim.2021.102743

22. Kuo CC, Wang CC, Chang WL, Liao TC, Chen PE, Tung TH. Clinical effects of baduanjin qigong exercise on cancer patients: A systematic review and meta-analysis on randomized controlled trials. *Evid Based Complement Alternat Med* (2021) 2021:6651238. doi: 10.1155/2021/6651238

23. *Health qigong management center of general administration of sport of China: Health qigong-baduanjin*. Beijing, China: People's Sports Publishing House of China (2003).

24. Kobayashi D, Kodera Y, Fujiwara M, Koike M, Nakayama G, Nakao A. Assessment of quality of life after gastrectomy using EORTC QLQ-C30 and STO22. *World J Surg* (2011) 35(2):357–64. doi: 10.1007/s00268-010-0860-2

25. Henry NL, Giles JT, Ang D, Mohan M, Dadabhoy D, Robarge J, et al. Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. *Breast Cancer Res Treat* (2008) 111:365–72. doi: 10.1007/s10549-007-9774-6

26. Morales L, Neven P, Timmerman D, Christiaens MR, Vergote I, Limbergen VE, et al. Acute effects of tamoxifen and third-generation aromatase inhibitors on menopausal symptoms of breast cancer patients. *Anticancer Drugs* (2004) 15 (8):753–60. doi: 10.1097/00001813-200409000-00003

27. Desai K, Mao JJ, Su I, Demichele A, Li Q, Xie SX, et al. Prevalence and risk factors for insomnia among breast cancer patients on aromatase inhibitors. *Support Care Cancer* (2013) 21(1):43–51. doi: 10.1007/s00520-012-1490-z

28. Bedard G, Zeng L, Zhang L, Lauzon N, Holden L, Tsao M, et al. Minimal important differences in the EORTC QLQ-C30 in patients with advanced cancer. *Asia Pac J Clin Oncol* (2014) 10(2):109–17. doi: 10.1111/ajco.12070

29. Horneber M, Fischer I, Dimeo F, Ruffer JU, Weis J. Cancer-related fatigue: epidemiology, pathogenesis, diagnosis, and treatment. *Dtsch Arztebl Int* (2012) 109 (9):161–71;quiz 72. doi: 10.3238/arztebl.2012.0161

30. Berger AM, Gerber LH, Mayer DK. Cancer-related fatigue: implications for breast cancer survivors. *Cancer* (2012) 118(8 Suppl):2261–9. doi: 10.1002/cncr.27475

31. Schmidt ME, Chang-Claude J, Vrieling A, Heinz J, Flesch-Janys D, Steindorf K. Fatigue and quality of life in breast cancer survivors: temporal courses and long-term pattern. *J Cancer Surviv* (2012) 6(1):11–9. doi: 10.1007/s11764-011-0197-3

32. Jiang YH, Tan C, Yuan S. Baduanjin exercise for insomnia: A systematic review and meta-analysis. *Behav Sleep Med* (2017), 1–13. doi: 10.1080/15402002.2017.1363042

33. Danforth DN. The role of chronic inflammation in the development of breast cancer. *Cancers (Basel)* (2021) 13(15): 3918. doi: 10.3390/cancers13153918

34. Collado-Hidalgo A, Bower JE, Ganz PA, Cole SW, Irwin MR. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. *Clin Cancer Res* (2006) 12(9):2759–66. doi: 10.1158/1078-0432.CCR-05-2398

35. Bauml J, Chen L, Chen J, Boyer J, Kalos M, Li SQ, et al. Arthralgia among women taking aromatase inhibitors: is there a shared inflammatory mechanism with co-morbid fatigue and insomnia? *Breast Cancer Res* (2015) 17:89. doi: 10.1186/s13058-015-0599-7

36. Bower JE, Irwin MR. Mind-body therapies and control of inflammatory biology: A descriptive review. *Brain Behav Immun* (2016) 51:1–11. doi: 10.1016/j.bbi.2015.06.012

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 21 September 2022
DOI 10.3389/fonc.2022.847400



OPEN ACCESS

EDITED BY
Julio de la Torre,
Comillas Pontifical University, Spain

REVIEWED BY
Marco Invernizzi,
University of Eastern Piedmont, Italy
Eleonora Anna Mess,
Wroclaw Medical University, Poland
Nigus Yimer,
Woldia University, Ethiopia

*CORRESPONDENCE
Changying Chen
changying@zzu.edu.cn
Panpan Wang
wangpanpan@zzu.edu.cn

SPECIALTY SECTION
This article was submitted to Breast Cancer, a section of the journal Frontiers in Oncology

RECEIVED 02 January 2022
ACCEPTED 24 August 2022
PUBLISHED 21 September 2022

CITATION
Getu MA, Chen C, Addissie A, Seife E, Wang P and Kantelhardt EJ (2022) A pilot study of cognitive behavioural therapy integrated with activity pacing for fatigued breast cancer patients undergoing chemotherapy in Ethiopia. *Front. Oncol.* 12:847400. doi: 10.3389/fonc.2022.847400



# A pilot study of cognitive behavioural therapy integrated with activity pacing for fatigued breast cancer patients undergoing chemotherapy in Ethiopia

Mikiyas Amare Getu[1,2,3], Changying Chen[1,2*], Adamu Addissie[4,5], Edom Seife[6], Panpan Wang[7*] and Eva Johanna Kantelhardt[4,8]

[1]Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [2]Department of Clinical Nursing, School of Nursing and Health, Zhengzhou University, Zhengzhou, China, [3]Global Health Working Group, Martin-Luther-University, Halle (Saale), Germany, [4]Institute of Medical Epidemiology, Biostatistics and Informatics, Martin-Luther-University, Halle (Saale), Germany, [5]School of Public Health, Department of Preventive Medicine, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia, [6]Tikur Anbessa Specialized Hospital, Department of Oncology, College of Health Science, Addis Ababa University, Addis Ababa, Ethiopia, [7]Department of Community Health Nursing, School of Nursing and Health, Zhengzhou University, Halle (Saale), Germany, [8]Department of Gynecology, Martin-Luther-University, Halle (Saale), Germany

**Background:** Fatigue is a common symptom in breast cancer patients, and it is one of the major factors that influence the quality of life (QoL). Cognitive behavioural therapy (CBT) has been recommended to manage cancer-related fatigue. In this study, CBT will be integrated with activity pacing (AP), which can help breast cancer patients achieve a balance between activity and rest. Therefore, this pilot study aimed to investigate the acceptability, feasibility, and efficacy of the CBT-AP intervention.

**Methods:** A total of 10 fatigued breast cancer patients undergoing chemotherapy were included in the study. The acceptability and feasibility of the study were measured by the patient recruitment rate, attrition rate, intervention fidelity, intervention compliance, and therapist's and participant's evaluations of the intervention. The outcomes were measured at baseline and at 6 weeks of intervention.

**Results:** The pre–post study suggested that CBT-AP was found to be acceptable and feasible for fatigued breast cancer patients undergoing chemotherapy. Among 27 eligible participants, 10 (37.03%) participants accepted our invitation to participate in the study. One participant dropped out from the intervention because of serious illness, and the dropout rate was 10%.Both the intervention fidelity and intervention compliance were found to be satisfactory.Fatigue severity [Brief Fatigue Inventory (BFI)] was reduced in

77.77% of participants from baseline to 6 weeks of intervention. The global health status/QoL scale and physical, emotional, and social functioning scales were improved from baseline to 6 weeks of intervention. All symptom scales, except constipation, diarrhea, and financial difficulties, were decreased after the intervention. Depression [Public Health Questionnaire (PHQ)-9] was reduced in 55.55% of participants.

**Conclusion:** This study suggested that CBT-AP is an acceptable, feasible, and potentially efficacious intervention to reduce fatigue and improve the QoL of breast cancer patients. The efficacy of a CBT-AP programme is going to be investigated in subsequent larger randomized clinical trials.

KEYWORDS

**breast cancer, cognitive behavioural therapy, fatigue, quality of life, depression, pilot study**

## Introduction

Breast cancer was the most commonly diagnosed cancer and the leading cause of cancer death among women worldwide in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases. The incidence and mortality age-standardized rate in Eastern Africa for female breast cancer patients in 2020 were 33% and 17.9%, respectively. Breast cancer is currently the most common type of cancer in Ethiopia with an estimated 16,133 (20.9%) new cases annually and 5-year prevalence of 48.52 per 100,000 (1, 2).

Breast cancer treatment and morbidity related to the disease might present disabling complications on physical functioning, psychological functioning, and behavioural attributes (3) that adversely affect the quality of life (QoL) of cancer patients (4, 5). Patients undergoing chemotherapy most commonly experienced fatigue, pain, and other symptoms (6).

A study conducted in Ethiopia on the QoL of breast cancer patients receiving chemotherapy showed poor QoL among breast cancer patients as compared to other international findings (5). Fatigue, pain, anxiety, and depression are some of the most common problems that occur in breast cancer patients, which negatively affect the QoL of breast cancer patients (7, 8).

Fatigue is a common symptom in breast cancer patients, and it was experienced by 80% of individuals who receive chemotherapy and/or radiotherapy (8–10). A study conducted in Ethiopia among breast cancer patients showed that fatigue is one of the major factors that influence the QoL of breast cancer patients (5).

Breast cancer patients might develop psychological distress and sleep disturbances during the diagnosis, treatment, and posttreatment periods, which negatively influence the QoL (11). A recently conducted systematic review and meta-analysis showed that the global prevalence of depression among breast cancer patients was 32.2%, which is higher in middle-income countries than in developed countries (12). A study conducted in Ethiopia about the prevalence of depression among breast cancer patients reported that one in four (25%) patients had depression. The depression could have a negative impact on adherence to treatment, overall QoL, and survival of the patient (13).

Effective interventions to reduce fatigue and psychological distress during cancer treatment are urgently needed that have potential to improve physical, emotional, and psychological health and overall QoL, as well as to relieve some of the financial burden related to the treatment (14).

Pharmacological interventions such as chemotherapy lead to a wide spectrum of treatment-related disabling complications, such as breast cancer-related lymphedema, pain, bone loss, arthralgia, and fatigue. Therefore, non-pharmacological therapies such as complementary therapies are recommended to reduce disease- and treatment-related symptoms, improve functioning, and improve adherence to treatment and long-term survival of patients (15, 16). To our knowledge, there were no structured non-pharmacologic interventions so far for breast cancer patients and survivors in the center.

Psychosocial interventions specifically designed to treat fatigue were significantly effective in reducing fatigue among cancer patients during cancer treatment (17) and after cancer

**Abbreviations:** AP, activity pacing; BFI, Brief Fatigue Inventory; CBT, cognitive behavioural therapy; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30; TASH, Tikur Anbessa Specialized Hospital; NCCN, National Comprehensive Cancer Network; PHQ, Public Health Questionnaire; QoL, quality of life; SD, standard deviation.

treatment (18). A meta-analysis study has reported the effectiveness of exercise and psychological interventions in reducing fatigue, and it is significantly better than the available pharmaceutical options. The most effective type of psychological intervention for reducing fatigue was cognitive behavioural therapy (CBT) (19).

The National Comprehensive Cancer Network (NCCN) has recommended CBT to combat cancer-related fatigue (20). CBT is a type of psychological treatment that is effective in managing fatigue (21), anxiety, and depression (22, 23). CBT for insomnia was effective in improving fatigue, anxiety, depression, and QoL (24). In addition, supervised physical exercise was recommended to reduce fatigue and improve the QoL (25).

No previous study has been done to investigate the effect of CBT combined with activity pacing (AP) on breast cancer patients undergoing chemotherapy. Some of the studies were conducted on cancer patients (21), and other studies were conducted on CBT without including AP and did not evaluate cancer-related fatigue as a primary outcome (22, 26). In this study, CBT was integrated with AP (CBT-AP). CBT-AP is based on both the cognitive behavioural theory and energy envelope theory. CBT identifies and replaces dysfunctional thoughts into correct thoughts. The intervention works by acting on the precipitating and perpetuating factors of fatigue (27). In order to act on the precipitating and perpetuating factors, there are different CBT strategies that were used to modify dysfunctional thoughts. These were cognitive restructuring, problem-solving, and coping strategies. The modified thought will bring favourable behaviour and action (28).

AP achieves a balance between activity and rest by energy management. AP enhances physical function and QoL by monitoring energy, fatigue, and activity levels and then modifying daily activities that reduce fatigue and improve the QoL (29). A personalized physical activity schedule has been proven to be effective in combating the adverse reaction of cancer treatment, reducing complications and decreasing mortality due to breast cancer (4).

CBT-AP is hypothesized to be an effective intervention because fatigue is a multidimensional construct (30). Most previous interventional studies conducted on CBT have been carried out on breast cancer survivors (21, 24, 27, 31). However, this study was conducted in patients with early and advanced stages of breast cancer. The earlier treatment of fatigue during chemotherapy is very important because it may assist women not only by decreasing fatigue during cancer treatment but also for treatment adherence. It provides women with evidence-based strategies during their earlier treatment trajectory that they can continue to use after cancer treatment and into survivorship (32, 33). Therefore, it will be a pioneering study that will assess the feasibility and efficacy of CBT-AP among breast cancer patients receiving chemotherapy. The finding of the study will be very helpful to revise the study protocol (33) for the subsequent definitive trial and assess the preliminary efficacy of CBT-AP.

This pilot study aimed to investigate the acceptability, feasibility, and preliminary efficacy of CBT-AP among breast cancer patients undergoing chemotherapy. We hypothesized that the intervention would be feasible and participants would demonstrate greater improvement in fatigue, depression, and QoL at 6 weeks of intervention.

Our research questions were as follows:

1. What is the recruitment and attrition rate?
2. Does the therapist adhere to the intervention protocol?
3. What is the therapist's and participant's evaluation of the intervention?
4. Is there any adverse event or serious adverse reactions during the intervention?
5. What is the preliminary efficacy of the intervention?

# Methods

## Design

This is a single-arm pilot study of the CBT-AP Trial (33) that was designed to assess the feasibility, acceptability, and potential efficacy of the intervention. The study was registered at the Pan-African Clinical Trial Registry on 24 August 2020 (PACTR202008881026130). The study has been reported in line with the CONSORT statement (34).

## Participants and study setting

Participants were recruited from Tikur Anbessa Specialized Hospital, Oncology Center and Day-Care Centre, in Addis Ababa, the capital city of Ethiopia from January to June 2021. The sample size was calculated to be 10 by considering 10% of the sample size of the main study.

The inclusion criteria were female breast cancer patients aged 18 years and above who were experiencing severe fatigue (overall rating 7 or more out of 10) for a week or more period on the Fatigue Severity Scale and was non-relapsed in any stage of the disease undergoing chemotherapy.

The exclusion criteria were patients who could not speak Amharic and patients with psychiatric illness or uncontrolled medical illness. Patients were screened by an oncologist for various types of clinically relevant systemic diseases or somatic causes that could result in fatigue (e.g., anaemia, malnutrition, hypothyroidism, and other physical comorbidities). If the fatigue had a somatic cause or was a systemic disease and it was confirmed by the oncologist, the patient did not participate in the study.

The eligibility criteria for the main trial are the same as those for the pilot study.

Consent forms and completed questionnaires were returned directly to the researcher in stamped addressed envelopes (the consent form and the questionnaire were returned in separate envelopes to protect confidentiality). Patients were told that participation was not mandatory.

## Patient recruitment and procedures

Breast cancer patients were invited to participate in the study through brochures and flyers. The names and contact addresses of eligible patients were recorded on the information sheet by the oncologist. When initial eligibility criteria were met, women were contacted by telephone to explain CBT-AP and the study procedures and to confirm their willingness to invest the requested time and effort.

Informed consent was taken from eligible patients who agreed to participate in the study. The participants answered four sets of Amharic version questionnaires as a baseline assessment: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (35), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Specific Module-45 EORTC QLQ-BR45 (36), Brief Fatigue Inventory (BFI)-9 (37), and PHQ-9 (38). The data collector recorded the sociodemographic and clinical characteristics of the patients from their medical records.

The CONSORT diagram indicating patient flow is depicted in Figure 1.

## CBT-AP intervention

The intervention included goal setting, AP, coping strategies, cognitive restructuring, dysfunctional thought management, sleep hygiene, relaxation skills, social support, and realizing goals.

The intervention protocol is developed according to the precipitating and perpetuating factors of fatigue. These include deregulation of activity, dysfunctional cognition, deregulation of the sleep–wake pattern, lack of coping with cancer and its treatment, fear of disease recurrence, and poor social interactions. Furthermore, AP was included in the intervention that is used to encourage patients to avoid exacerbations of fatigue and other symptoms.

The intervention had six sessions: three face-to-face sessions (first, fourth, and sixth sessions) and three telephone sessions (second, third, and fifth sessions). Each session consisted of

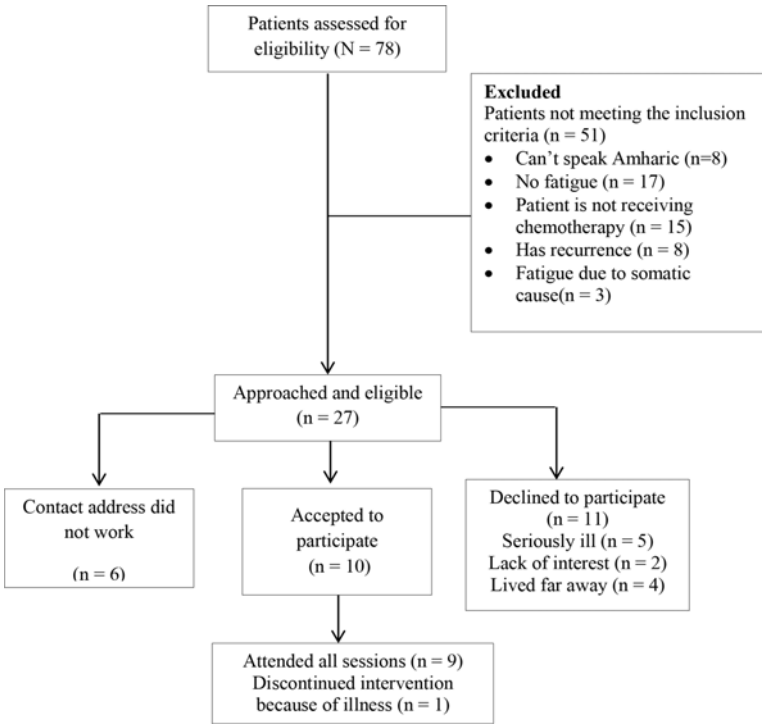



FIGURE 1
Cognitive behavioural therapy integrated with activity pacing (CBT-AP) patient recruitment CONSORT diagram.

homework assignments to complete before the next session. The therapists gave instructions on how to do the homework assignments for every session. The manual for the participants and therapists and worksheets for the assignments were prepared and given to the therapists and participants. At the beginning of each session, a revision was done and the participant's worksheets were evaluated for completion. The intervention was provided by a trained clinical psychologist and oncology nurse.

Therapists completed a 2-day workshop delivered by the developer of CBT-AP.

The average time for the face-to-face sessions was 2 h, while it was 35 min for the telephone sessions. The skill of the interventionist was examined by a standardized checklist.

## Intervention sessions

### Session 1

During this session, introduction of the therapist and participants and setting of the ground rules for individual and group sessions were made. Introductory information was provided about the disease and its treatment as well as the CBT-AP framework. Progressive muscle relaxation and deep breathing exercises (abdominal breathing) were demonstrated to the participants.

### Session 2

The participants set SMART—specific, measurable, achievable, and time-bound—goals.

AP was used to balance activity and rest to avoid exacerbation of fatigue.

### Session 3

Sleep pattern disturbances were managed by maintaining sleep hygiene, avoiding sleeping during the day, and adhering to fixed bedtimes and wake-up times (27, 39).

The participant's dysfunctional thoughts about breast cancer and its treatment were assessed.

### Session 4

In this session, participants learnt about cognitive restructuring, which is used to replace unhelpful or dysfunctional thoughts into helpful thoughts. In addition, the therapist explained about coping mechanisms for anxiety, depression, and other diagnosis- and treatment-related problems (40).

### Session 5

In this session, individual dysfunctional thought management and social support were carried out. The therapist challenged the participant's dysfunctional thoughts and replaced them with positive/functional thoughts.

### Session 6

All previous sessions were reviewed, and goals were checked for their achievement. An action plan was prepared to maintain the behaviour.

Details of the intervention are available elsewhere (33).

The content of the CBT-AP outline is shown in Table 1.

## Timing of assessments

Sociodemographic and clinical characteristics, QoL, fatigue, and depression were measured at baseline and after 6 weeks (end of CBT-AP).

## Feasibility outcomes

The feasibility of the outcome was measured by patient recruitment rate, intervention fidelity, intervention compliance, and therapist's evaluation of the intervention. The acceptability of the intervention was measured by participant's evaluation of the intervention. The criteria for feasibility of outcomes were considered to be 20% recruitment and attrition rate. A minimum of attending four sessions is the threshold for feasibility to represent sufficient exposure to benefit from the intervention.

## Recruitment rate

Recruitment rate was calculated by dividing the number of enrolled patients by the number of eligible patients.

## Intervention fidelity

The feasibility outcomes were evaluated based on intervention fidelity and compliance with the programme. A standardized checklist was used to assess intervention fidelity and compliance.

Acceptability was measured based on the participants' evaluations of the intervention. The intervention fidelity of the therapy was monitored by an assessor. All face-to-face sessions and telephone sessions were recorded after getting consent from participants. The assessor rated the intervention fidelity using a standardized fidelity checklist. The intervention fidelity was scored on a scale from 0 (poor) to 5 (excellent) based on the following criteria: 1) The content of the session was covered; 2) Group/individual discussion points were raised and discussed very well; 3) An explanation was given about the homework, and

TABLE 1 Cognitive behavioural therapy integrated with activity pacing (CBT-AP) outline for breast cancer patients undergoing chemotherapy.

| Session | Operational procedures | Main themes | Wks. | Delivery | Duration |
|---|---|---|---|---|---|
| 1 | Introduction and setting ground rules<br>Breast cancer, chemotherapy and fatigue Explain CBT framework<br>Relaxation | Introduction of therapist and participants<br>Setting ground rules.<br>Describe breast cancer, chemotherapy, and fatigue.<br>Participants describe experiences of fatigue.<br>Introduce CBT-AP framework and how it manages fatigue and improves the QoL.<br>Introduction to progressive muscle relaxation exercise and deep breathing exercises. | First | Face-to-face | 2 h |
| 2 | Goal setting<br>Activity pacing | Set realistic goals.<br>Counsel about activity pacing, barriers of activity pacing, managing energy, assess prioritizing daily activities based on available energy and establishing baseline activity. | Second | Telephone | 20 min |
| 3 | Managing of sleep disturbances<br>Dysfunctional thoughts | Participants identify sleep habits that improve sleep disturbances.<br>Prescribe routine bed time.<br>Consult about sleep hygiene.<br>Identify participant's dysfunctional thoughts about breast cancer, its treatment, and fatigue. | Third | Telephone | 20 min |
| 4 | Cognitive restructuring<br>Coping mechanisms | Reformulate dysfunctional cognitions regarding breast cancer, its treatment, fatigue and fear of disease recurrence.<br>Identify reasonable and unreasonable thinking.<br>Coping mechanism to decrease stress, anxiety, depression and treatment side effects. | Fourth | Face-to-face | 2 h |
| 5 | Individual dysfunctional thought management<br>Improve social support | Counsel on how an individual changes dysfunctional thoughts.<br>Explain how to communicate about fatigue with others.<br>Support system and interpersonal communication.<br>Modify unhelpful cognition about social environment and expectations. | Fifth | Telephone | 20 min |
| 6 | Realizing goals | Evaluation of the progress with respect to the goal<br>Action plan for maintaining cognitive behavioural change | Sixth | Face-to-face | 2 h |

the therapist strongly recommended them to read the module and do their homework; 4) The time taken was within the proposed range; 5) The participants were given the opportunity to explain their ideas; 6) The participants were interested and actively participating in the session; 7) The participants did their homework; and 8) The participants attended sessions on time during the face-to-face/telephone sessions.

The checker was a registered psychiatric nurse with a clinical experience of 7 years and trained on the CBT-AP intervention.

In order to increase the intervention fidelity, the intervention provider was provided with a therapist intervention manual that included all materials necessary to effectively deliver the intervention.

## Participant's evaluation of the therapy

Upon completion of the programme, the participants were asked to complete a short evaluation that included statements about their satisfaction with different elements of the programme as assessed by a 4-point Likert scale: "not at all", "a little", "quite a bit", and "very much". In total, 14 statements were presented.

## Intervention outcomes

### Primary outcome measure

#### Fatigue

Fatigue was measured by the Brief Fatigue Inventory Amharic version (BFI-Amh) (37). The BFI consists of nine items asking patients whether they felt unusually fatigued in the last week. The BFI-Amh showed good acceptability, internal reliability (Cronbach's $\alpha$ = 0.97), construct, and concurrent validity (37).

### Secondary outcome measures

#### Quality of life

**EORTC QLQ-C30**

It is a reliable and valid measure of the QoL of cancer patients. It consists of 30 items arranged with five functional scales, three symptom scales, and a global health and QoL scale. According to scoring procedures, the QLQ-C30 was transformed to scores ranging from 0 to 100. Higher scores represent a better level of functioning on the functional and single-item scales. A higher score of symptom scales represents a higher level of symptoms for the symptom scales (35). The score of each item ranged from 1 (not at all) to 4 (very much).

**EORTC QLQ-BR45**

The updated version of the EORTC QLQ-BR23 incorporated an additional 22 items that contain a target symptom scale and satisfaction scale (36). The EORTC QLQ-BR45 had good internal reliability (α = 0.80), test–retest reliability (α = 0.77), and validity. The score of each item ranged from 1 (not at all) to 4 (very much).

### Depression

The PHQ-9 is a short tool used to assess depression. The Amharic version of the PHQ-9 demonstrated good internal reliability (α = 0.81), test–retest reliability (α = 0.92), and validity results (38). The score of each item ranged from 0 (not at all) to 3 (nearly every day). The total score ranges from 0 to 27 (41).

This pilot study is not blinded. So, the analysis was done by the principal investigator who is a PhD student in Nursing. However, the randomized controlled trial (RCT) that we have conducted after the pilot study was blinded for the outcome assessors and statistician. Therefore, an independent statistician who was blind to the treatment allocation did the data analysis.

## Statistical analysis

Statistical analysis was principally descriptive, and the frequency, mean, and standard deviation (SD) were calculated. We assessed the acceptability of CBT-AP by the therapist's and participant's evaluations of the intervention and number of CBT-AP sessions attended.

The feasibility of the study was assessed in terms of recruitment rate into the study (number agreeing to participate out of those approached), attrition rate, and adherence to and compliance with the intervention. The preliminary efficacy of the therapy was examined by differences before and after the intervention, and data from all participants (N = 9) were analysed using descriptive statistics such as frequency, mean, and SD.

## Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the ethics committees of the Zhengzhou University IRB (number: ZZURIB 2020-10; Date: 18 June 2020) and Addis Ababa University, College of Health Science teaching hospital (number: 101/20/Onco; Date: 28 October 2020). The patients/participants provided their written informed consent to participate in this study.

# Results

## Demographic and clinical characteristics

In total, 10 women participated in the study. Nine (90%) patients completed all sessions. Participants had a mean age of 38.3 years, SD = 7.23.

The majority (80%) of participants had undergone surgery, 20% had hormonal therapy, and 50% had received surgery and chemotherapy. Half of the participants (50%) had secondary education. Half of the participants were housewives. Majority (90%) of the participants were living in an urban area.

Most of the participants (50%) had a stage III tumour, and the histological classification of the tumour for all participants was ductal carcinoma (Table 2).

## Participant's evaluation of the therapy

All participants (100%) reported having received sufficient information about breast cancer, treatment approach, and benefits of the therapy. Most women reported that they had sufficient progress after the intervention (88.9%) and had more control over their symptoms after the therapy (66.7%). Most of the qualities of the therapist, such as expertise, trustworthiness, punctuality, and respectfulness, were evaluated positively (100%). Most women were satisfied with the module (66.7%), thought their treatment was relevant and the correct approach (100%), and telephone session was easily delivered and understandable (100%). Moreover, the participants advised others patients to attend this therapy (100%) (Table 3).

## Therapist's evaluation of the therapy

The therapists were generally satisfied with the content of the therapy but suggested to revise the Amharic translation of a few vague words in the module and to increase the telephone session duration from 20 min to 30–35 min. Session 1 took 2 h and 40 min, which is longer than the proposed time. They have also suggested including "brainstorming" questions at the beginning of every module in which the participants could actively participate and give reflection on the concepts of the session. Appendices "C" and "H" of the worksheets were suggested for revision to be more easily understood by the participants.

## Feasibility of the intervention

### Recruitment

A total of 78 patients were assessed for eligibility. Of those assessed for eligibility, 51 patients did not meet the inclusion

10.3389/fonc.2022.847400

TABLE 2 Baseline sociodemographic and clinical characteristics of breast cancer patients undergoing chemotherapy.

| Variables | Frequency | Percentage |
|---|---|---|
| Age<br>Mean (SD) | 38.3 (7.2) | |
| **Educational status** | | |
| No formal education | 2 | 20 |
| Primary education | 1 | 10 |
| Secondary education | 5 | 50 |
| Above secondary education | 2 | 20 |
| **Occupational status** | | |
| Housewife | 5 | 50 |
| Government employed | 1 | 10 |
| Merchant | 1 | 10 |
| Daily labourer | 3 | 30 |
| **Religion** | | |
| Orthodox Christianity | 8 | 80 |
| Muslim | 1 | 10 |
| Protestant | 1 | 10 |
| **Residence** | | |
| Urban | 9 | 90 |
| Rural | 1 | 10 |
| **Marital status** | | |
| Single | 3 | 30 |
| Married | 3 | 30 |
| Divorced | 2 | 20 |
| Widowed | 2 | 20 |
| **Stage of tumour** | | |
| Stage I | 1 | 10 |
| Stage II | 2 | 20 |
| Stage III | 5 | 50 |
| Stage IV | 2 | 20 |
| **Cancer treatment** | | |
| Chemotherapy | 10 | 100 |
| Surgery | 8 | 80 |
| Radiotherapy | 0 | 0 |
| Hormonal therapy | 2 | 20 |
| Surgery + Hormonal therapy + Chemotherapy | 2 | 20 |
| Surgery + Chemotherapy | 5 | 50 |
| **Monthly income (ETB)** | | |
| ≤2,000 | 7 | 70 |
| 2,001–3,000 | 1 | 10 |
| >3,000 | 2 | 20 |
| **ECOG-PS** | | |
| ECOG I | 7 | 70 |
| ECOG II | 2 | 20 |
| ECOG III | 1 | 10 |
| ECOG IV | 0 | 0 |
| **Chemotherapy cycle** | | |
| 1–4 | 6 | 60 |
| 5–8 | 4 | 40 |
| **Comorbidity** | | |
| Yes | 4 | 40 |
| No | 6 | 60 |

*(Continued)*

TABLE 2 Continued

| Variables | Frequency | Percentage |
|---|---|---|
| **Time since diagnosis (month)** | | |
| 1–6 | 6 | 60 |
| 7–12 | 4 | 40 |

SD, standard deviation; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; ETB, Ethiopian birr.

criteria, leaving 27 patients eligible. Among the 27 eligible participants, 10 (37.03%) participants accepted our invitation to participate in the study, and the recruitment rate was 37.03%. The remaining 17 patients did not participate in the study because six of them had contact addresses that were unreachable and 11 of them declined to participate in the study. Reasons for declining participation included being seriously ill (n = 5), lack of interest (n = 2), and living too far away (n = 4).

## Intervention fidelity

The intervention fidelity and intervention compliance were satisfactory. According to the standardized checklist, all of the session content and objectives were well addressed (100%). The group/individual discussion points were discussed very well, and an explanation was given about the homework (100%).

The participant's punctuality (73.3%) and therapy session were within the proposed time range (66.7%). Completion of homework by participants was not applicable during sessions 1 and 6. In the other sessions, the completion rate of homework by participants was 50%.

## Intervention compliance

Intervention compliance was defined as the number of sessions completed and time spent in each session of the therapy. The study participants were expected to attend six sessions. Among 10 patients, seven patients attended all (100%) of the sessions. Two patients attended four (66.7%) sessions and missed another two sessions because of illness. One participant dropped out from the intervention because of serious illness, and the dropout rate was 10%. There were 54 sessions in total for these nine patients. Upon completion of the study, 50 (93%) out of 54 expected sessions had been completed by nine participants. A missed session was replaced by another telephone session within 5 working days. Therefore, the overall compliance rate by session was 93%.

TABLE 3 Participant's evaluation of the intervention among breast cancer patients.

| Information | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|
| I received sufficient information about breast cancer, types of treatment, treatment side effects, and management. | _ | _ | _ | 100 |
| I have received sufficient information about the benefits of the therapy. | _ | _ | _ | 100 |
| **Experienced effect** | | | | |
| I had sufficient progress after the intervention. | _ | _ | 11.1 | 88.9 |
| Because of the intervention, I had control over my symptoms. | _ | 11.1 | 22.2 | 66.7 |
| **Therapist** | | | | |
| The therapists had sufficient expertise and delivered all sessions successfully. | _ | _ | _ | 100 |
| I trusted the therapists. | _ | _ | _ | 100 |
| The therapists were respectful. | _ | _ | _ | 100 |
| The therapists were punctual. | _ | _ | _ | 100 |
| The therapists were interested in me and my opinion. | _ | _ | 22.2 | 77.8 |
| The therapists provided an immediate response to emergency situations. | _ | _ | _ | 100 |
| The therapists explained the content of the session at the beginning of each session. | _ | _ | 11.1 | 88.9 |
| **Other** | | | | |
| I am satisfied with the module prepared for the participants. | _ | _ | 33.3 | 66.7 |
| The telephone session was easily delivered and understandable. | _ | _ | _ | 100 |
| The treatment was relevant and the correct approach for my symptoms. | _ | _ | _ | 100 |
| I would advise others to follow this therapy. | _ | _ | _ | 100 |

## Outcome measures

### Primary outcome measure

#### Fatigue

Fatigue severity (BFI-9) decreased in 77.77% of subjects from a mean of 7.40 ( ± 2.21) at baseline to 3.50 ( ± 1.94) at 6 weeks of intervention (P ≤ 0.05) (Figure 2; Table 4).

## Secondary outcome measures

### Quality of life

#### EORTC QLQ-C30

The global health QoL scale and physical, emotional, and social functioning scales were improved from baseline to 6 weeks of intervention (Figure 3).

All symptom scales, except constipation, diarrhea, and financial difficulties, were decreased after the intervention (Figure 2; Table 4).

The effect of CBT-AP on EORTC QLQ-C30 functioning and symptom score is shown in Table 4.

#### EORTC QLQ BR45

Body image, future perspective, and breast satisfaction functioning scales were improved after the intervention. All symptom scales except upset by hair loss and endocrine sexual scales were decreased from baseline to 6 weeks of intervention.

A reduction in the symptom scale (fatigue, pain, dyspnea, insomnia, and appetite loss) was reported (Figure 4).

### Depression

Depression measured by PHQ-9 was reduced in 55.55% of participants from a total mean score of 1.20 ( ± 0.76) at baseline to 0.70 ( ± 0.51) after intervention (Figure 2; Table 4).

### Adverse events

There were no adverse events or serious harm that occurred during the intervention.

# Discussion

## Feasibility of intervention

The cancer tumor-related factors and its treatment lead to disabling complications such as fatigue and pain that will directly affect the QoL.

This is the first study conducted to evaluate the feasibility of CBT-AP and to provide preliminary data about its effect on fatigue, depression, and QoL among breast cancer patients. In this study, CBT-AP was found to be a feasible and potentially efficacious intervention for breast cancer patients undergoing chemotherapy. Another study conducted on cancer patients had shown that self-help workbook intervention was feasible in cancer patients receiving chemotherapy, although the effect of the intervention was limited (42). The discrepancy between the effects of intervention might be because the intervention was guided by a trained therapist in this study.

The intervention fidelity and the intervention compliance were satisfactory according to the checklist. Participants' attendance to each session was good, with seven participants among 10 who attended all of the sessions (100%). Two patients attended four (66.7%) sessions. We considered attendance at a minimum of four sessions to represent sufficient exposure to benefit from the intervention.

However, the percentage of participants who completed their homework/worksheet (a type of task used to exercise CBT-AP on a daily basis) at each session was relatively low (50%). The main

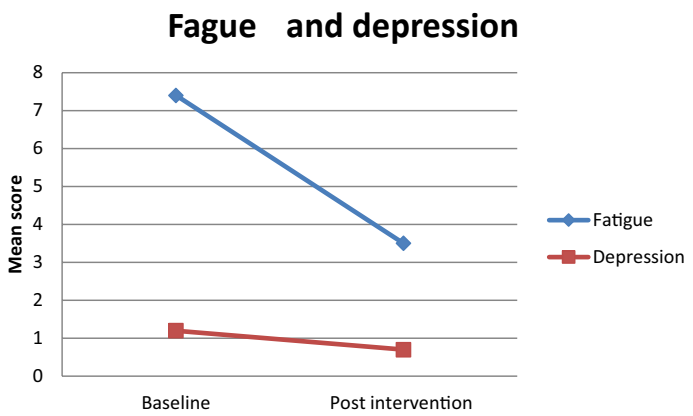



FIGURE 2
Estimated mean trajectories of fatigue and depression among breast cancer patients.

TABLE 4 The effect of Cognitive behavioural therapy integrated with activity pacing (CBT-AP) on fatigue, depression, and quality of life of breast cancer patients undergoing chemotherapy.

| EORTC QLQ-C30Domain/Symptom | Baseline | | Posttest | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| Global | 116.7 | 61.8 | 137.0 | 41.5 |
| Physical | 48.9 | 27.5 | 63.7 | 26.5 |
| Role | 99.3 | 17.7 | 75.9 | 29.0 |
| Emotional | 61.1 | 27.6 | 78.7 | 27.9 |
| Cognitive | 70.4 | 27.4 | 70.4 | 18.6 |
| Social | 66.7 | 39.1 | 77.8 | 25.0 |
| Fatigue | 70.4 | 27.7 | 39.5 | 28.4 |
| Nausea and vomiting | 59.3 | 45 | 42.6 | 37.4 |
| Pain | 72.2 | 38.2 | 35.2 | 33.8 |
| Dyspnea | 37.0 | 48.43 | 18.5 | 29.4 |
| Insomnia | 48.1 | 37.7 | 29.6 | 35.1 |
| Appetite loss | 66.7 | 44.1 | 33.3 | 28.9 |
| Constipation | 22.2 | 28.9 | 25.9 | 36.4 |
| Diarrhea | 11.1 | 23.6 | 11.1 | 23.6 |
| Financial difficulties | 44.4 | 47.1 | 59.2 | 46.5 |
| **EORTC QLQ-BR45 Domain/Symptom** | | | | |
| Body image | 70.4 | 22.5 | 87 | 27.4 |
| Sexual functioning | 98.1 | 5.5 | 98.1 | 5.5 |
| Sexual enjoyment | 100 | 0.0 | 100 | 0.00 |
| Future perspective | 40.7 | 40 | 74.1 | 43.4 |
| Systematic therapy side effect | 52.4 | 22.3 | 39.7 | 16 |
| Breast symptom | 29.6 | 24.3 | 25.9 | 18.4 |
| Arm symptom | 37 | 28.3 | 22.2 | 19.2 |
| Upset by hair loss | 50 | 35.6 | 81.5 | 37.7 |
| Breast satisfaction scale | 51.8 | 46.7 | 75.9 | 40.1 |
| Endocrine therapy scale | 31.5 | 15.6 | 22.2 | 11.9 |
| Endocrine sexual scale | -29.6 | 11.1 | -29.6 | 11.1 |
| Skin mucosis scale | 21.6 | 15.8 | 17.3 | 13.7 |
| **Fatigue (BFI-9)** | 7.40 | 2.21 | 3.50 | 1.94 |
| **Depression (PHQ-9)** | 1.20 | 0.76 | 0.70 | 0.51 |

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core30; EORTC QLQ-BR45, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire- Breast Cancer Specific Questionnaire45; BFI-9, Brief Fatigue Inventory-9; PHQ-9, Patient Health Questionnaire- 9; SD, Standard deviation.

reasons mentioned by the patients were being "unable to comprehend the instructions for the homework/worksheets and some vague words" and illnesses during the therapy. Revision was recommended on the worksheet instructions and the replacement of a few words for easy understanding in the main trial. The time allowed for session 1 (face-to-face) and all of the telephone sessions was inadequate. Therefore, the telephone session was suggested to be delivered for 30–35 min, and session 1 was suggested to be delivered in two sessions.

The participant's punctuality for the face-to-face session was not satisfactory. This might be due to participants residing far from the centre where the therapy was delivered and lack of adequate transportation. Therefore, the participants should be informed over the telephone 1 day earlier than the face-to-face session about the time schedule and to get well prepared for early transportation access.

Some patients declined to participate in the study after recruitment due to lack of interest, living too far away, longer therapy sessions, and unable to reach their contact addresses. Future efforts should focus on explaining about the benefits of participating in the study before requesting informed consent, taking additional contact address, and scheduling interventions and evaluations for the same day as chemotherapy sessions to optimize patient participation and to avoid declining to participate. Other strategies should be suggested to increase the number of participants and prevent dropout, such as regularly calling patients weekly to strengthen their participation and minimize the dropout rate (43).

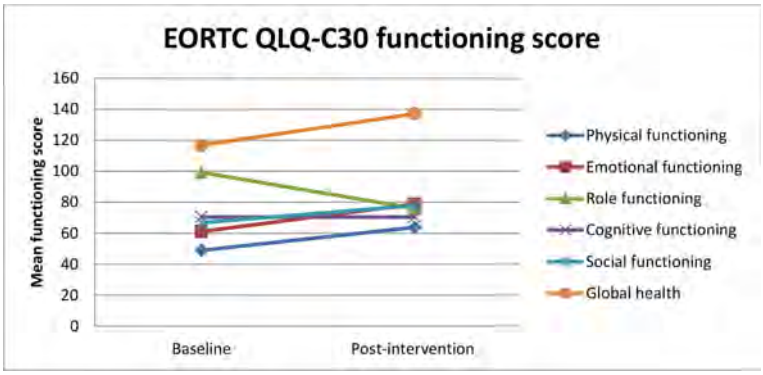



FIGURE 3
Estimated mean trajectories of quality of life functioning scores among breast cancer patients.

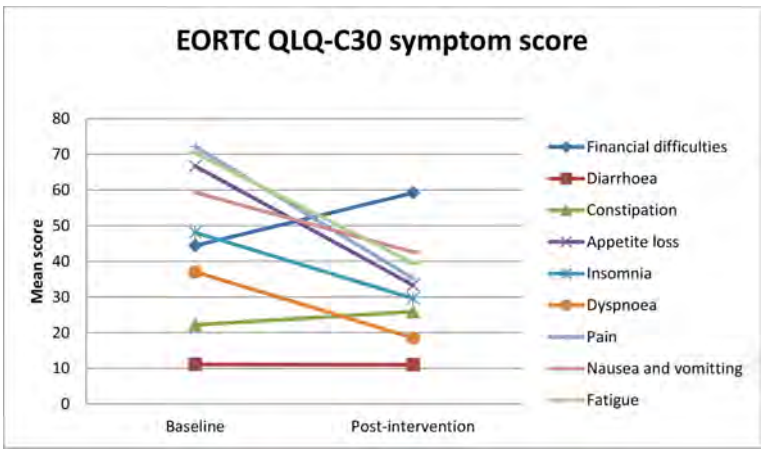



FIGURE 4
Estimated mean trajectories of quality of life symptom scores among breast cancer patients.

## Efficacy of CBT-AP

Our pilot study showed that breast cancer patients undergoing chemotherapy who received our novel CBT-AP intervention demonstrated decreased fatigue from baseline (mean = 7.40, SD ± 2.21) to 6 weeks of intervention (mean = 3.50, SD ± 1.94) as measured by BFI-9, and EORTC QLQ-C30 fatigue scale showed decreased fatigue (from a mean = 70.4, SD ± 27.7, to a mean = 39.5, SD ± 28.4). These results demonstrate the preliminary efficacy of our novel CBT-AP as an active fatigue intervention. This is consistent with previous studies done on the effect of CBT among cancer patients (39, 44) and cancer survivors (21). Similarly, another study showed that rehabilitative physical exercise was found to be safe, feasible, and effective to reduce fatigue (45). This can be explained by increased functioning scales, and decreased symptom scales contributed to the reduction of fatigue. In this study, the effect of CBT-AP on the QoL might be attributed to the reduction of fatigue. These results highlighted that the effect of CBT-AP in reducing fatigue had contributed to improve the QoL of breast cancer patients. Contrary to this study, a systematic review and meta-analysis of physical therapies showed no effect on the reduction of fatigue. This might be due to heterogeneity of the included studies (46).

Invernizzi et al. (45) revealed the preliminary efficacy of rehabilitative activity in improving EORTC QLQ-C30 functional score and global health status score and reduction of EORTC QLQ-C30 symptom scales. In this study, physical function, emotional function, social function, and global health status/QoL subscales were improved after intervention. Similarly, another study showed improvement in the social and emotional functioning scale of EORTC QLQ-C30 (23). Zhu XY, Li Z, Chen C, et al. (46) found that a meta-analysis showed that physical therapies improved the

overall QoL of breast cancer patients. Fatigue, pain, dyspnea, insomnia, and appetite loss were decreased from baseline to post intervention, which is in agreement with previous studies conducted on the effects of psycho-education on breast cancer patients (23). Moreover, CBT had shown improvements on fatigue from baseline to 15 months of therapy (47).

According to this study, an increase in functioning scales and decrease in symptom scales of EORTC QLQ-C30 and EORTC QLQ-BR45 might contribute to reducing fatigue among breast cancer patients.

The findings of this study showed that constipation, diarrhea, and financial difficulties were increased from baseline to 6 weeks of intervention. This can be explained by the fact that CBT-AP is not a valid intervention for constipation and diarrhea. Similarly, there is no financial-related content in the intervention sessions; thus, it may not be valid for financial difficulties too. Previous studies have shown the efficacy of CBT for depression in breast cancer patients (48, 49). In this study, there was a minimal decrease in the depression scale. This might be due to the small sample size in this study. The forthcoming trial will consider implementing different ways to improve the patient recruitment rate, participant retention, and compliance with the intervention. The efficacy of a CBT-AP programme is going to be investigated in larger RCTs.

CBT-AP is safe and can be feasibly implemented within the standard of care for the future larger trial. CBT-AP shall be integrated to routine cancer care based on the findings of the main trial.

## Strengths and limitations

While this study produced intriguing results on the preliminary efficacy of the new intervention, there are several important limitations to note. The limitation of this pilot study was the small sample size, which could not allow us to conduct statistical analysis of the differences between the baseline and 6 weeks of intervention for fatigue, depression, and QoL variables and decreased the generalizability of the findings. Other previous pilot studies had also faced small sample sizes (50, 51). The small sample size in this study was due to the nature of the study (a pilot) and lack of eligible participants.

We would emphasize that these results need to be interpreted with caution because of the design of pre–post pilot study with a small sample size and the limited length of observation time. However, the findings of the study were sufficiently promising to justify conducting an RCT, which we are currently doing.

Comorbidities and their medication that may affect the outcome were not included into the questionnaire. Since those are rare in the population, we expect little bias.

The recruitment rate was found to be low. Therefore, modification of the recruitment method is recommended in the subsequent trial. Tracking system should be established for each of the individuals to improve the recruitment rate and recruiters to follow each individual through the entire process. It is also recommended to explain the study in more detail, i.e., benefits and risks of participation to improve their interest to participate, answer patient's questions, tracking with an alternative phone number to solve unreachable address, to cover the transportation cost for those who lived far away, and increase the recruitment period to achieve an adequate sample size.

# Conclusion

The findings of this study indicated relevant improvement of fatigue from baseline to 6 weeks of intervention. CBT-AP was found to be a safe, feasible, and potentially efficacious intervention to reduce fatigue and improve the QoL of breast cancer patients. The results of our prospective randomized clinical trial will provide more definitive information regarding the efficacy of the intervention.

# Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

# Ethics statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the ethics committees of the Zhengzhou University IRB (number: ZZURIB 2020-10; Date: 18 June 2020) and Addis Ababa University, College of Health Science teaching hospital (number: 101/20/Onco; Date: 28 October 2020). The patients/participants provided their written informed consent to participate in this study.

# Author contributions

MG is responsible for the conception and design of the study. CC, EK, ES, and AA have been supervising the overall activities and provided valuable comments. MG, CC, EK and WP have been involved in data analysis, and interpretation. All authors contributed to the article and approved the submitted version.

# Funding

This work was supported by Else-Kroener-Foundation through Martin-Luther-University, Halle-Wittenberg,

Germany [grant No. 2018_HA31SP]. The funding body did not have any role in the study design, data collection, analysis and interpretation of data, and in writing the manuscript. The open-access publication fee is received from Zhengzhou University, School of Nursing and Health.

## Acknowledgments

We express our gratitude to the patients who participated in this study. We are also grateful to Addis Ababa University, College of Health Science for arranging a room to deliver the therapy to the patients.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020 : GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660

2. American cancer society. *Breast cancer facts and figures 2019-2020*. Atlanta: American Cancer Society (2019).

3. Campbell KL, Pusic AL, Zucker DS, McNeely ML, Binkley JM. A prospective model of care for breast cancer rehabilitation: Function. *Cancer* (2012) 118(8 suppl):2300–11. doi: 10.1002/cncr.27464

4. Zaidi S, Hussain S, Verma S, Veqar Z, Khan A, Nazir SU, et al. Efficacy of complementary therapies in the quality of life of breast cancer survivors. *Front Oncol* (2018) 7. doi: 10.1097/SMJ.0b013e3181c38c41

5. Mohammed A, Taye G, Gizaw M, Hussien M. Quality of life and associated factors among patients with breast cancer under chemotherapy at tikur anbessa specialized hospital, Addis Ababa, Ethiopia. *PloS One* (2019) 14(9):1–13. doi: 10.1371/journal.pone.0222629

6. Kaya T, Karatepe AG, Günaydn R, Yetiş H UA. Disability and health- related quality of life after breast cancer surgery: Relation to impairments. *South Med J* (2010) 103(1):37–41. doi: 10.1097/SMJ.0b013e3181c38c41

7. Montazeri A, Vahdaninia M, Harirchi I, Ebrahimi M, Khaleghi F, Jarvandi S. Quality of life in patients with breast cancer before and after diagnosis: An eighteen months follow-up study. *BMC Cancer* (2008) 8(1):330. doi: 10.1186/1471-2407-8-330

8. Wondie Y, Hinz A. Quality of life among Ethiopian cancer patients. *Support Care Cancer* (2020) 28(11):5469–78. doi: 10.1007/s00520-020-05398-w

9. Sibhat SG, Fenta TG, Sander B, Gebretekle GB. Health-related quality of life and its predictors among patients with breast cancer at tikur anbessa specialized hospital. *Health Qual Life Outcomes* (2019) 17(165):1–10. doi: 10.1186/s12955-019-1239-1

10. World Health Organization. *What is fatigue or weakness?* (2020). Available at: https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/fatigue/what-is-cancer-related-fatigue.html (Accessed 2020 Apr 25).

11. Pitman A, Suleman S, Hyde N, Hodgkiss A. Depression and anxiety in patients with cancer. *BMJ* (2018) 361:1–6. doi: 10.1136/bmj.k1415

12. Pilevarzadeh M, Amirshahi M, Afsargharehbagh R, Rafiemanesh H, Hashemi S-M, Balouchi A, et al. Global prevalence of depression among breast cancer patients: A systematic review and meta-analysis. *Breast Cancer Research and Treatment* (2019) 176(3):519–33. doi: 10.1007/s10549-019-05271-3

13. Wondimagegnehu A, Abebe W, Abraha A, Teferra S. Depression and social support among breast cancer patients in Addis Ababa, Ethiopia. *BMC Cancer* (2019) 19(1):1–8. doi: 10.1186/s12885-019-6007-4

14. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: The scale of the problem. *Oncologist* (2007) 12(Suppl 1):4–10. doi: 10.1634/theoncologist.12-S1-4

15. Invernizzi M, de Sire A, Venetis K, Cigna E, Carda S, Borg M, et al. Quality of life interventions in breast cancer survivors: State of the art in targeted rehabilitation strategies. *Anticancer Agents Med Chem* (2021) 22:801–10. doi: 10.2174/1871520621666210609095602

16. Michelotti A, Invernizzi M, Lopez G, Lorenzini D, Nesa F, De SA, et al. Tackling the diversity of breast cancer related lymphedema : Perspectives on diagnosis, risk assessment, and clinical management. *Breast* (2019) 44:15–23. doi: 10.1016/j.breast.2018.12.009

17. Mm G, Mfm G, Cahhvm V. Psychosocial interventions for reducing fatigue during cancer treatment in adults (Review). *Cochrane Database Syst Rev* (2009) 1):1–56. doi: 10.1002/14651858.CD006953.pub2

18. Corbett TK, Groarke A, Devane D, Carr E, Walsh JC, Mcguire BE. The effectiveness of psychological interventions for fatigue in cancer survivors: Systematic review of randomised controlled trials. *Syst Rev* (2019) 8(324):1–30. doi: 10.1186/s13643-019-1230-2

19. Mustian KM, Alfano CM, Heckler C, Kleckner AS, Kleckner IR, Leach CR, et al. Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: A meta-analysis. *JAMA Oncol* (2017) 3(7):961–8. doi: 10.1001/jamaoncol.2016.6914

20. Berger AM, Mooney K, Banerjee C, Breitbart WS. Cancer-related fatigue version. *NCCN guideline.* (2018), 1–64.

21. Van Gessel LD, Abrahams HJG, Prinsen H, Bleijenberg G, Heins M, Twisk J, et al. Are the effects of cognitive behavior therapy for severe fatigue in cancer survivors sustained up to 14 years after therapy? *J Cancer Surviv* (2018) 12(4):519–27. doi: 10.1007/s11764-018-0690-z

22. Qiu H, Ren W, Yang Y, Zhu X, Mao G, Mao S, et al. Effects of cognitive behavioral therapy for depression on improving insomnia and quality of life in Chinese women with breast cancer: Results of a randomized, controlled, multicenter trial. *Neuropsychiatr Dis Treat* (2018) 14:2665–73. doi: 10.2147/NDT.S171297

23. Wu P, Chen S, Huang W, Chang S, Hsu M. Effects of a psychoeducational intervention in patients with breast cancer undergoing chemotherapy. *J Nurs Res* (2018) 26(4):266–79. doi: 10.1097/jnr.0000000000000252

24. Dirksen SR, Epstein DR. Efficacy of an insomnia intervention on fatigue, mood and quality of life in breast cancer survivors. *J Adv Nurs* (2008) 61(6):664–75. doi: 10.1111/j.1365-2648.2007.04560.x

25. Meneses-Echávez JF, González-Jiménez E, Ramírez-Vélez R. Effects of supervised exercise on cancer-related fatigue in breast cancer survivors: A systematic review and meta-analysis. *BMC Cancer* (2015) 15(1):1–13. doi: 10.1186/s12885-015-1069-4

26. Xu Y, Zhu F, Wu J. The efficacy of cognitive behavioral therapy to treat depression and anxiety and improve quality of life among early- stage breast cancer patients. *Integr Cancer Ther* (2019) 18(1):1–9. doi: 10.1177/1534735419829573

27. Gielissen MFM, Verhagen S, Witjes F, Bleijenberg G. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with

patients waiting for cognitive behavior therapy: A randomized controlled trial. *J Clin Oncol* (2006) 24(30):4882–7. doi: 10.1200/JCO.2006.06.8270

28. Corbett T, Walsh JC, Groarke A. Cancer-related fatigue in post-treatment cancer Survivors : Theory-based development of a web-based intervention. *JMIR Cancer* (2017) 3(2):1–13. doi: 10.2196/cancer.6987

29. Friedberg F, Krupp LB. A comparison of cognitive behavioral treatment for chronic fatigue syndrome and primary depression. *Clin Infect Dis* (1994) 18 (Supplement_1):S105–10. doi: 10.1093/clinids/18.Supplement_1.S105

30. Ahlberg K, Ekman T, Fannie Gaston-Johansson VM. Assessment and management of cancer-related fatigue in adults. *Lancet* (2003) 362:640–50. doi: 10.3109/9781420052909.002

31. Peoples AR, Garland SN, Pigeon WR, Perlis ML, Wolf JR, Heffner KL, et al. Cognitive behavioral therapy for insomnia reduces depression in cancer survivors. *J Clin Sleep Med* (2019) 15(1):129–37. doi: 10.5664/jcsm.7586

32. Bean HR, Stafford L, Little R, Diggens J, Ftanou M, Alexander M, et al. Light-enhanced cognitive behavioural therapy for sleep and fatigue: Study protocol for a randomised controlled trial during chemotherapy for breast cancer. *Trials* (2020) 21(1):1–14. doi: 10.1186/s13063-020-4196-4

33. Getu MA, Chen C, Wang P, Yohannes E, Seife E, Panpan C. Study protocol of CBT-AP Trial : A randomized controlled trial of cognitive behavioral therapy integrated with activity pacing for fatigued breast cancer patients undergoing chemotherapy. *Integr Cancer Ther* (2021) 20:1–12. doi: 10.1177/15347354211032268

34. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L. CONSORT 2010 statement: Extension to randomised pilot and feasibility trials. *BMJ* (2016) 355:1–28. doi: 10.1136/bmj.i5239

35. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* (1993) 85(5):365–76. doi: 10.1093/jnci/85.5.365

36. Bjelic-Radisic V, Cardoso F, Cameron D, Brain E, Kuljanic K, Costa R, et al. An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients: EORTC QLQ-BR45. *Ann Oncol* (2020) 31(2):283–8. doi: 10.1016/j.annonc.2019.10.027

37. Gebremariam GT, Anshabo AT, Tigeneh W, Engidawork E. Validation of the amharic version of the brief fatigue inventory for assessment of cancer-related fatigue in Ethiopian cancer patients. *J Pain Symptom Manage* (2018) 56(2):264–72. doi: 10.1016/j.jpainsymman.2018.04.015

38. Gelaye B, Williams MA, Lemma S, Deyessa N, Bahretibeb Y, Shibre T, et al. Validity of the patient health questionnaire-9 for depression screening and diagnosis in East Africa. *Psychiatry Res* (2013) 210(2):653–61. doi: 10.1016/j.psychres.2013.07.015

39. Sandler CX, Goldstein D, Horsfield S, Bennett BK, Friedlander M, Bastick PA, et al. Randomized evaluation of cognitive-behavioral therapy and graded exercise therapy for post-cancer fatigue. *J Pain Symptom Manage* (2017) 54(1):74–84. doi: 10.1016/j.jpainsymman.2017.03.015

40. Abrahams HJG, Gielissen MFM, Goedendorp MM, Berends T, Peters MEWJ, Poort H, et al. A randomized controlled trial of web-based cognitive behavioral therapy for severely fatigued breast cancer survivors (CHANGE-study): Study protocol. *BMC Cancer* (2015) 15(1):1–10. doi: 10.1186/s12885-015-1787-7

41. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. *J Gen Intern Med* (2001) 16(9):606–13. doi: 10.1046/j.1525-1497.2001.016009606.x

42. Takano T, Matsuda A, Ishizuka N, Ozaki Y, Suyama K, Tanabe Y, et al. Effectiveness of self-help workbook intervention on quality of life in cancer patients receiving chemotherapy: results of a randomized controlled trial. *BMC Cancer* (2021) 21(1):1–9. doi: 10.1186/s12885-021-08333-2

43. Palesh O, Solomon N, Hofmeister E, Jo B, Shen H, Cassidy-eagle E, et al. A novel approach to management of sleep-associated problems in patients with breast cancer ( MOSAIC ) during chemotherapy : A pilot study. *Sleep J* (2020) 43:1–11. doi: 10.1093/sleep/zsaa070

44. Abrahams HJG, Gielissen MFM, Donders RRT, Goedendorp MM, van der Wouw AJ, Verhagen CAHHVM, et al. The efficacy of Internet-based cognitive behavioral therapy for severely fatigued survivors of breast cancer compared with care as usual: A randomized controlled trial. *Cancer* (2017) 123(19):3825–34. doi: 10.1002/cncr.30815

45. Invernizzi M, de Sire A, Lippi L, Venetis K, Sajjadi E, Gimigliano F, et al. Impact of rehabilitation on breast cancer related fatigue: A pilot study. *Front Oncol* (2020) 10:1–7. doi: 10.3389/fonc.2020.556718

46. Zhu X, Li Z, Chen C, Feng R, Cheng B, Liu R. Physical therapies for psychosomatic symptoms and quality of life induced by aromatase inhibitors in breast cancer Patients : A systematic review and meta-analysis. *Front Oncol* (2021) 11:1–16. doi: 10.3389/fonc.2021.74528047

47. Irwin MR, Olmstead R, Carrillo C, Sadeghi N, Nicassio P, PA G, et al. Tai chi chih compared with cognitive behavioral therapy for the treatment of insomnia in survivors of breast cancer: A randomized, partially blinded, noninferiority trial. *J Clin Oncol* (2017) 35(23):2656–65. doi: 10.1200/JCO.2016.71.0285

48. Gudenkauf LM, Antoni MH, Stagl JM, Lechner SC, Jutagir DR, Bouchard LC, et al. Brief cognitive – behavioral and relaxation training interventions for breast Cancer : A randomized controlled trial. *J Consult Clin Psychol* (2015) 83 (4):677–88. doi: 10.1037/ccp0000020

49. Ren W, Qiu H, Yang Y, Zhu X, Zhu C, Mao G, et al. Randomized controlled trial of cognitive behavioural therapy for depressive and anxiety symptoms in Chinese women with breast cancer. *Psychiatry Res* (2019) 271:52–9. doi: 10.1016/j.psychres.2018.11.026

50. Zhang M, Chen J, Zhang T, Wang Q, Li H. Feasibility and effect of a guided self-disclosure intervention designed to facilitate benefit finding in breast cancer patients : A pilot study. *Eur J Oncol Nurs* (2021) 50:1–7. doi: 10.1016/j.ejon.2020.101879

51. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Med Res Methodol* (2010) 67(10):1–7. doi: 10.1186/1471-2288-10-67

# Frontiers in Oncology

**Advances knowledge of carcinogenesis and tumor progression for better treatment and management**

The third most-cited oncology journal, which highlights research in carcinogenesis and tumor progression, bridging the gap between basic research and applications to imrpove diagnosis, therapeutics and management strategies.

---

## Discover the latest Research Topics

See more →


**Frontiers**

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

**Contact us**

+41 (0)21 510 17 00
frontiersin.org/about/contact