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Turkish Federation of Breast Diseases Societies

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Société Internationale de Sénologie

Senologic International Society

Global Federation of Breast Healthcare Societies

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European Journal of Breast Health

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European Journal of Breast Health

European Journal of Breast Health

Aims and Scope

The European Journal of Breast Health (Eur J Breast Health) is an international, scientific, open access periodical published by independent, unbiased, and double-blinded peer-review principles journal. It is the official publication of the Turkish Federation of Breast Diseases Societies, and the Senologic International Society (SIS) is the official supporter of the journal.

The European Journal of Breast Health is published quarterly in January, April, July, and October. The publication language of the journal is English.

EJBH aims to be a comprehensive, multidisciplinary source and contribute to the literature by publishing manuscripts with the highest scientific level in the fields of research, diagnosis, and treatment of all breast diseases; scientific, biologic, social and psychological considerations, news and technologies concerning the breast, breast care and breast diseases.

The journal publishes original research articlesreviews, letters to the editor, brief correspondences, meeting reports, editorial summaries, observations, novel ideas, basic and translational research studies, clinical and epidemiological studies, treatment guidelines, expert opinions, commentaries, clinical trials and outcome studies on breast health, biology and all kinds of breast diseases, and very original case reports that are prepared and presented according to the ethical guidelines.

TOPICS within the SCOPE of EJBH concerning breast health, breast biology and all kinds of breast diseases:

Epidemiology, Risk Factors, Prevention, Early Detection, Diagnosis and Therapy, Psychological Evaluation, Quality of Life, Screening, Imaging Management, Image-guided Procedures, Immunotherapy, molecular Classification, Mechanism-based Therapies, Carcinogenesis, Hereditary Susceptibility, Survivorship, Treatment Toxicities, and Secondary Neoplasms, Biophysics, Mechanisms of Metastasis, Microenvironment, Basic and Translational Research, Integrated Treatment Strategies, Cellular Research and Biomarkers, Stem Cells, Drug Delivery Systems, Clinical Use of Anti-therapeutic Agents, Radiotherapy, Chemotherapy, Surgery, Surgical Procedures and Techniques, Palliative Care, Patient Adherence, Cosmesis, Satisfaction and Health Economic Evaluations.

The target audience of the journal includes specialists and medical professionals in surgery, oncology, breast health and breast diseases.

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Case Report	1000	200	15	No tables	10 or total of 20 images
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Current Opinion	300	No abstract	5	No tables	No media

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Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

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Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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Review

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Treatment Changes in Breast Cancer Management and De-Escalation of Breast Surgery

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ABSTRACT

A better understanding of tumor biology and new drugs have led to significant changes in the management of breast cancer (BC). Radical mastectomy, which had been the treatment for BC for more than a century, was based on the hypothesis that BC is a local-regional disease. In the 1970s, Fisher's studies showed that cancer cells could reach the systemic circulation without passage through the regional lymphatic system. Multidisciplinary treatment of BC, which was now considered a systemic disease, was started and radical mastectomy was replaced by breast-conserving surgery (BCS)+, axillary dissection (AD), systemic chemotherapy, hormonotherapy, and radiotherapy in early-stage BC. Modified radical mastectomy, chemotherapy, and radiotherapy were applied as a treatment for locally advanced BC. However, later clinical studies demonstrated that the breast can be preserved in those who respond well to neo-adjuvant chemotherapy (NAC). In the early 1990s, sentinel lymph node biopsy (SLNB) in early-stage BC (cN0) was performed using blue dye and radioisotope markers. It was shown that AD may be avoided in SLN-negative patients, and SLNB has been a standard intervention in cN0 patients. In this way, the very serious complications of AD, especially lymphedema, were avoided. BC has been shown to be a heterogeneous disease and the tumor may be divided into four different molecular subtypes. Thus, optimal treatment differed from patient to patient (one size fits all was inappropriate), individualized treatments have emerged and over-treatment was avoided. The prolongation of life expectancy and the decrease in recurrence led to an increase in the rate of BCS, an acceptable cosmetic result with oncoplastic surgery, and a better quality of life. The increase in the rate of complete response to NAC with new and targeted agents and especially in human epidermal growth factor receptor-2+ and triple-negative patients with a poor prognosis has led to the use of NAC regardless of cN0. The complete disappearance of the tumor after NAC has been reported by some studies, suggesting that breast surgery may not be needed. However, other studies have shown that vacuum biopsies performed on the tumor bed have a high rate of false negativity. Therefore, it is difficult to suggest that there is no need for lumpectomy, which is cheaper and safer today. The false negativity rate of SLNB is high in patients with cN1 at the time of diagnosis and cN0 after NAC (approximately 13%). In order to reduce this rate to ≤5%, clinical studies have recommended the use of the dual method, marking the positive lymph node before chemotherapy and removing 3–4 nodules with SLN. In summary, a better understanding of tumor biology and new drugs have changed the management of BC and de-escalate the role of surgical treatment.

Keywords: Breast cancer management, surgery, chemotherapy, sentinel lymph node biopsy, molecular subtypes

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Key Points

- Breast cancer management
- Surgery
- Chemotherapy
- Sentinel lymph node biopsy
- Molecular subtypes

Today, modern breast cancer treatment uses a multimodal approach that combines surgery, radiotherapy, systemic therapy and immunotherapy. The aim is to apply these different treatments according to the demographic, clinical and pathological characteristics of the patients and the tumor and to obtain a good cosmetic outcome while maintaining oncological safety.

We can evaluate the changes in the biology and treatment of breast cancer under three different hypothesis headings. These are: I. Local-

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Regional Disease Hypothesis, II. Systemic Disease Hypothesis, III. Intermediate Hypothesis. These three hypotheses will be reviewed in detail below.

I. Local Regional Disease Hypothesis (Halstedian Hypothesis)

The Halstedian paradigm, the first hypothesis of breast cancer (BC) biology, guided BC treatment for nearly a century (1). Halsted thought that cancer in the breast first invaded local tissues and lymph nodes and then spread to distant organs. He defined radical mastectomy (RM) as the removal of the skin of the breast, pectoral muscles, lymphatic ducts and ipsilateral lymph nodes. In the article containing 50 patients, he showed that he reduced the local recurrence rate to 6%, in contrast to his colleagues in the same period (1). Although RM provided a high rate of local control, there was no evidence that it provided better survival. In addition, this intervention had significant morbidities, such as arm edema, loss of arm function, loss of body image and psychological morbidities. Following his work on lymphatic anatomy, Gray reported in 1939 that the deep fascia on the pectoral major muscle lacked lymphatic ducts (2). As a result of the serious thoracic deformity and other complications of RM and Gray's research, Patey and Dyson (3) defined modified radical mastectomy (MRM) including preservation of the pectoralis major muscle. By comparing 118 patients with RM and MRM, they showed that MRM was as effective as RM in the treatment of BC and had less morbidity (3). They also showed that partial mastectomy and axillary dissection may be performed in small tumors, but the risk of local recurrence may be high, so axillary radiotherapy can be added to simple mastectomy, but radiotherapy may be more harmful than axillary dissection. After these studies, MRM became the first-choice surgical procedure (4).

II. Systemic Disease Hypothesis (Fisherian Hypothesis)

The lack of an increase in survival despite the adoption of a radical surgical intervention led scientists to conduct new research into the biology of BC. Bernard Fisher revealed that BC may be a systemic disease at the beginning of his experimental and clinical studies (5). He reported that cancer cells entering the bloodstream during the formation of the tumor migrated to distant organs and metastasized systemically. According to Fisher, hematogenous spread in particular did not necessarily involve lymph nodes. Thus regional lymph nodes may not have been the first monitors of distant metastases but were a potential focus for dissemination of the disease depending on the tumor-patient relationship (6). Experimental studies have shown that tumor cells can pass trans-nodally into the systemic circulation. His results invalidated the notion that lymph nodes are passive filters, showing that cancer cells can go directly to the lymph ducts as well as pass directly into the bloodstream through lymphatic-venous collaterals. The systemic disease hypothesis showed that BC treatment should be multidisciplinary, and chemotherapy and radiotherapy should be added to surgical treatment and this concept has been widely accepted.

Long-term results of combined chemotherapy [cyclophosphamide, methotrexate, and 5-Fluorouracil (CMF)], which was published by Bonadonna (7, 8) in 1973 for the systemic treatment of BC, showed that CMF given once a month and for 12 cycles after RM increased survival and disease-free survival in lymph node positive patients.

Endocrine therapy (ET) for BC is one of the first applications of individualized treatment for cancer. At the end of the 19th century, Sir George Thomas Beatson first discovered the positive effect of bilateral oophorectomy on the development of BC lesions in women with advanced disease, and ET was born (9). Research into antihormonal agents has shown that only patients with the expression of hormone receptors benefit from treatment with the selective estrogen receptor modulator, tamoxifen (9). This knowledge has led to the development of third-generation aromatase inhibitors (AI) such as anastrozole, letrozole and exemestane, to reduce estrogen levels in hormone-receptor-positive post-menopausal BC patients (10). ET (ovarian suppression, tamoxifen and AI) has been shown in clinical studies to increase survival and reduce recurrences in hormone receptor positive pre-menopausal patients (10-13).

Long-term results from the NSABP B-04 study compared simple mastectomy and RM interventions in patients with clinically negative axillae and showed that they had similar overall survival results (14). In the Milan study and in the NSABP-06 studies, patients who underwent total mastectomy and patients who received partial mastectomy + axillary lymph node dissection (ALND) and radiotherapy did not show comparable survival rates (15, 16). Thus, in early-stage BC, breast-conserving surgery (BCS) and radiotherapy have become a standard surgical intervention.

The occurrence of serious complications, especially lymphedema, in patients with ALND suggested that axillary dissection may be avoided in cN0 patients. In 1992, Morton performed a radioisotope and in 1994 Giuliano performed the sentinel lymph node biopsy (SLNB) using blue dye (17, 18). In clinical studies, it has been shown that other lymph nodes are also negative in patients diagnosed with early-stage BC (cN0) and SLN negative and axillary dissection is not required in these patients (19).

III. Intermediate Hypothesis

The 20-year follow-up results of the NSABP-B04 study suggested that the disease was local-regional as 36.8% of the patients survived without any systemic treatment (14). However, the presence of distant metastases in 24.5% of the patients and the occurrence of a very significant proportion of these within the first five years showed that BC is prone to spread systemically in some patients. These results show that BC is a heterogeneous cancer, varying between individual patients, that is, it tends to remain local-regional in some patients and systemic in others and this is known as the Intermediate Hypothesis.

The fact that BC remains as a local-regional disease in some patients and that it has a systemic spread while on a smaller scale in some patients suggests that there is an intermediate hypothesis that includes both earlier hypotheses in BC. Indeed, BC is heterogeneous and individual, and not every patient should be given RM, as in the Halsted hypothesis, or multidisciplinary treatment (one size fits all) should not be applied to every patient, as in the Fisher hypothesis. In some patients, even large BC tumors localized in the breast for a long time do not always metastasize systemically, while in other patients it can metastasize even when the tumor is very small.

We know that the biological behavior of BC and the response to treatments vary. In 2000, Perou et al. (20) published molecular portraits of human breast tumors in a paper published in Nature. Using complementary DNA microsequences representing 8,102 human genes, variations in gene expression patterns in 65 breast tumor samples from 42 different individuals were characterized. They showed that tumors can be divided into molecular subtypes such as Luminal A, Luminal B, human epidermal growth factor receptor-2 (HER-2) (+), Basal and Normal Basal Like, which are distinguished by

common differences in gene expression patterns. Today, the molecular subtypes of BC are generally evaluated into four groups: Luminal A; Luminal B; HER-2 (+); and triple-negative. The main purpose here is to apply personalized treatment according to the molecular structure of the cancer and to avoid over-treatment and its complications and economic losses.

New therapeutic drugs have also resulted in significant changes in the surgical treatment of BC, as they prolong life expectancy by reducing recurrence. In particular, there have been significant increases in the rate of BCS and preventive surgery has been performed in appropriate multifocal and multicentric cancers (21, 22). A good cosmetic appearance may be achieved by filling the cavity formed after lumpectomy with the surrounding breast tissue (volume displacement) or muscle tissue (volume displacement). During surgical intervention, the other breast is also operated to provide a symmetrical appearance. In patients who are pathological gene carriers, reconstruction is added to the opposite breast by prophylactic mastectomy.

The increased complete response to chemotherapy with modern drugs added to neoadjuvant chemotherapy (NAC) makes NAC a standard approach in patients with operable early-stage BC. NAC is the first choice, especially in those with HER-2 positive and triple negative molecular subtypes with poor prognosis. The objectives are to destroy the tumor cells that cannot be demonstrated by systemic screening by early initiation of systemic therapy, to assess the response to chemotherapy in vivo, to increase the rate of BCS by shrinking the tumor and to avoid axillary dissection by providing a negative axilla that was positive before treatment.

In patients who are thought to have a clinical and pathological complete response in the breast after NAC, some studies have been conducted only according to the results of vacuum biopsy including surgical intervention to the breast and treatment with radiotherapy (23, 24). In the MD Anderson study, the tumorous area was excised in patients who underwent clinically complete response and vacuum biopsy and false negative results were obtained in 5% of the patients (23). In other studies, false negativity rates ranged from 19% to 49% (24). In an ongoing prospective clinical study, triple-negative and HER-2 positive patients with negative vacuum biopsy after NAC were also given axillary radiotherapy and local recurrence was not observed during the 26.4-month follow-up period (25). However, the number of patients in the study was 31 and the follow-up period was short which should be considered limitations of this study and when considering the reported results. However, today there is no conclusive evidence to dispense with surgical treatment in patients with a full clinical response to NAC, and it is necessary to wait for the long-term results of high quality prospective clinical trials to decide. Breast surgery today is an easier and more economical procedure and should continue.

ALND, as mentioned earlier, may have very serious complications, especially lymphedema. ALND is avoided even in patients with limited axilla positivity in sentinel lymph nodes (26, 27).

In the ACOSOG Z0011 study, among women with T1 or T2 invasive primary BC, no palpable axillary lymph node, and 1 or 2 sentinel lymph nodes containing metastases, 10-year overall survival for patients treated with sentinel lymph node dissection alone was non-inferior to overall survival for those treated with ALND (26). These findings do not support routine use of ALND in this patient population based on 10-year outcomes. The AMAROS trial evaluated ALND versus axillary radiotherapy (ART) in patients with cT1-2, node-negative BC and a positive sentinel node (SN) biopsy (27). Ten-year analysis of this study confirms a low axillary local-recurrence rate after both ART and ALND with no difference in overall survival, disease free survival, and loco-regional control. Considering less arm morbidity, ART is preferred over ALND for patients with SN-positive cT1–2 BC.

Modern NAC regimens provide pathologic complete response (pCR) in a significant proportion of patients with node-positive BC (27-31). Axillary pCR response rates vary according to the molecular subtype of the tumor and the stage of the disease, and are 50-70% in HER-2 positive patients, 40–47% in triple negative patients and 15–21% in estrogen positive patients. SLNB is considered an important intervention to determine axillary pCR after NAC and to avoid ALND. However, the rate of false negativity after SLNB is around 13%, which necessitated some research to reduce this rate (32). In these studies, dual method, removal of three or more SLNs, immunohistochemical method, clip of positive lymph nodes, magnetic seed, radio isotope labeling and radar localization techniques were used and the false negativity rate was reduced to around 5% (32-35). Targeted axillary dissection was first descibed by the MD Anderson Cancer Center. In this technique, an iodine–125 seed was placed in the clipped node under ultrasound guidance 1 to 5 days before surgery, mapping agents, including radioisotope (technetium–99m sulfur colloid) and/or blue dye, were injected before or at the time of surgery. During surgery, a gamma probe on the iodine-125 setting was used to identify the seed-containing node, and the technetium-99m setting was used to identify SLNs. All nodes containing blue dye, radioactivity, or which were palpable were removed and labeled as SLNs (36, 37).

Conclusion

BC is the most common cancer in the world and the most common cause of death in women, and with screening, early diagnosis and effective modern treatments, it is possible to live a healthy life while preserving body integrity. Research has resulted in a combination of the hypotheses of BC, as a local and regional or systemic disease, requiring different treatment for each patient, but individual treatment according to the clinical and pathological molecular characteristics of the individual tumors. New treatment agents reduce not only systemic spread but also local regional recurrence in BC. Thus, radical surgery in BC has been replaced by surgical interventions that protect the breast and axilla as far as possible.

Significant changes have been seen in the treatment of BC as a result of a better understanding of the biology of the disease, the treatment of which has been guided only by surgeons for a very long time. Multicenter studies and meta-analyses involving breast surgeons have played an important role in this change. However, with the current understanding of BC, we can say that even in cases where complete breast and axillary response is thought to be obtained after NAC, it is too early to give up BC surgery, which is easy to apply and cost-effective. To achieve this, more effective chemotherapetic agents and more sensitive radiological methods are needed.

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Authorship Contributions

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Systematic Review

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Management and Outcomes of Metastatic and Recurrent Malignant Phyllodes Tumors of the Breast: A Systematic Literature Review

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ABSTRACT

To summarize the evidence on the current management and outcomes for metastatic and recurrent malignant phyllodes tumors (MPTs) of the breast. A systematic literature review of all cases of metastatic or recurrent MPTs of the breast published between 2010 and 2021 was performed. In total, 66 patients from 63 articles were included. Fifty-two (78.8%) had distant metastatic disease (DMD subgroup), and 21 (31.8%) showed locoregional recurrent/progressive disease (LRPR subgroup). Locoregional recurrences in patients with no distant metastases were treated with surgical excision in all cases. Radiotherapy was administered in 8/21 cases (38.1%) and was combined with chemotherapy in 2/21 cases (9.5%). Metastatic disease was managed through metastases surgical excision, chemotherapy, radiotherapy, or a combination of these three in 84.6% of cases, while the remaining patients received no oncological treatments. Chemotherapy was proposed in 75.0% of cases. Anthracycline and alkylating agent-based combination regimens were most frequently administered. The median survival time was 24 (2.0–152.0) months, and 72.0 (2.5–98.5) months in the DMD and LRPR subgroups, respectively. Management of recurrent or metastatic MPTs is challenging. Surgery is the fundamental approach, but the use of adjuvant radio- and chemo-therapy remains controversial due to the lack of scientific evidence. Further studies and international registers are needed to implement new and more efficient treatment strategies.

Keywords: Phyllodes tumor; breast cancer; recurrence; local relapse; metastatic; adjuvant treatment

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Key Points

- Evidence and guidelines concerning the management of malignant phyllodes tumors (MPTs) of the breast are limited, especially in the case of recurrent or metastatic disease.
- This study reports current trends in managing MPTs, confirming inconsistent management approaches and a lack of evidence supporting treatment plans.
- Further studies and international registers are needed to implement new and more efficient treatment strategies.

Introduction

Phyllodes tumors of the breast are rare fibroepithelial neoplasms, representing less than 1% of all breast tumors (1). They are classified into benign, borderline, and malignant phyllodes tumors (MPTs) based on histologic characteristics (2). The rarity of this malignancy contributes to the difficulty in defining the most appropriate treatment. This uncertainty is even more marked for recurrent and metastatic MPTs, for which prognosis is significantly affected, and evidence is limited concerning their optimal management. In this study, all cases of metastatic and/or recurrent MPTs published in the last decade were reviewed to give an overall view of their current management and outcomes.

Materials and Methods

Search Strategy and Selection Process

This systematic literature review was conducted using a structured search protocol based on the PRISMA criteria (3). To find all cases of metastatic or recurrent MPTs of the breast reported over the last decade, PubMed, Embase, and Web of Science were searched using the terms "malignant phyllode/malignant phyllodes," "tumor/tumors,"

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and "breast" for all articles published from 1st January 2010 and 31st December 2021. We included all articles in English or French reporting metastatic or recurrent phyllodes tumors of the breast. We excluded articles reporting benign or borderline phyllodes tumors, patients aged <18 years, phyllodes tumors in men, studies or case series without individual data, and articles with unavailable full text. Sixty-three articles were selected and analyzed (4-66). The literature search protocol design is summarized in Figure 1.

Data Collection Process and Analysis

Two authors performed data extraction independently, results were compared, and any conflict was discussed with a third party. For each patient, any relevant demographic and oncological data concerning the initial treatment, follow-up, management, and outcomes in cases of metastatic or recurrent phyllodes tumors of the breast was extracted. When possible, corresponding authors were contacted to obtain missing or updated information.

SPSS, v20 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Data were analyzed for the subgroups of patients presenting distant metastases at the time of diagnosis or as a progression/recurrence, designated the distant metastatic disease (DMD) subgroup and for those with locoregional progressive or recurrent disease, designated the locoregional progressive/recurrent (LRPR) subgroup. Since the difference between progression and recurrence was frequently difficult to clarify, these two entities were analyzed together. LRPR disease was considered to consist of lesions limited to the initially involved breast, skin, surgical scar, surrounding soft tissues, and ipsilateral thoracic wall (e.g., pectoral muscles), axillary and internal mammary lymph nodes, without any sign of distant metastases. DMD was considered in all cases presenting with lesions in any other location, with or without a concomitant LRPR disease. Patients who first presented with a locoregional progression/recurrence with no distant lesions that lately developed a metastatic disease were analyzed in both the LRPR and DMD subgroups. Continuous variables are presented as median with minimum and maximum values, and categorical variables as numbers and percentages (%). All missing information was considered as such, and no assumptions were made. Patients with missing data for a specific variable were not included in the statistical analysis. The Kaplan-Meier statistical method was applied for survival analysis, and the log-rank test was used to compare survival curves. Comparison between subgroups was not the objective of this study, but when reported, differences were compared using ANOVA, the Kruskal-Wallis test, or Fisher's exact test. A p-value <0.05 was considered statistically significant.

Results

In total, 66 patients from 63 series/case reports were included in the analysis. Fifty-two (78.8%) presented with a distant metastatic disease (DMD subgroup), and 21 (31.8%) showed locoregional recurrent/progressive disease (the LRPR subgroup). Seven patients first presented with locoregional progressions/recurrences with no distant lesions and

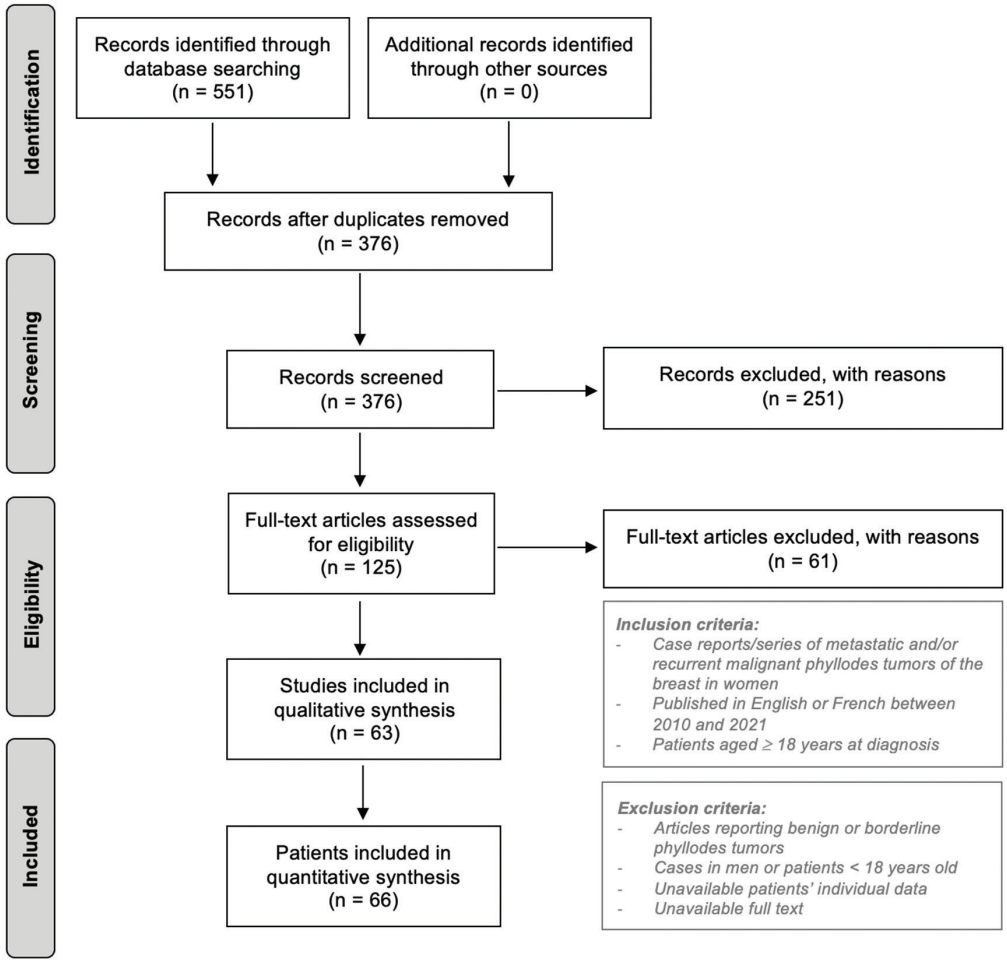

Figure 1. Selection flowchart showing the inclusion and exclusion process

later developed metastatic disease. These patients were analyzed in both the DMD and LRPR subgroups.

The median age was 50 (26–82) years in the DMD subgroup and 45 (18–82) years in the LRPR subgroup. The median tumor size was 100 (22–430) mm and 90 (30–300) mm in the DMD and LRPR subgroups, respectively. All except one patient (62/63, 94.4%) received primary breast surgery by mastectomy (51/63, 81.0%) or a lumpectomy (11/63, 17.5%). Histological characteristics, including surgical margin status, were reported in 25 patients (37.9%) and are summarized in Table 1. Following primary surgery, systemic chemotherapy was administered in 6/13 patients (46.2%) with distant metastasis at diagnosis and in 3/60 patients (5.0%) with no initial sign of metastatic disease. Chemotherapy was given as an adjuvant treatment except in one patient, who received neoadjuvant doxorubicin and cyclophosphamide before mastectomy for mass reduction (45). Adjuvant radiotherapy was administered in 1/13 patients (7.7%) with distant metastases at diagnosis and in 12/60 patients (20.0%) with no initial sign of metastases. Complementary data concerning initial observations and management are reported in Table 1.

Management of Locoregional Progressions/Recurrences

Locoregional progression/recurrence was observed in 21/21 patients (100%) in the LRPR subgroup and in 18/52 patients (34.6%) in the DMD subgroup. Overall, the median time after the initial breast surgery and the first locoregional progression/recurrence was 8.9 (1.0–36.0) months. No differences were observed between patients operated on by mastectomy or lumpectomy or relating to surgical margins status.

Locoregional progressions/recurrences in patients with no distant metastases were treated with surgical excision in all cases (21/21, 100%). Adjuvant radiotherapy was administered in 8/21 cases (38.1%) and was combined with chemotherapy in 2/21 cases (9.5%). In patients with associated distant metastases, locoregional lesions were surgically excised in 14/18 patients (77.8%). Adjuvant radiotherapy was given in 9/18 patients (50.0%) and was associated with adjuvant chemotherapy in 3/18 cases (16.7%).

Patients with initially limited locoregional recurrences/progressions (LRPR subgroup) subsequently developed distant metastases in 9/21 patients (42.9%) with a median interval between first local progression/recurrence and distant relapse of 2.0 (0.5–14.0) months.

Overall, multiple local progressions/recurrences were observed in 10 patients (15.9%), 4 patients (6.3%) presented with two progressions/recurrences, and 4 patients (7.9%) presented with more than two progressions/recurrences. The median interval between the first and the second and between the second and the third locoregional recurrences/progressions was 3.5 (0.5–40) months and 4 (0.5–14) months, respectively. All patients except three developed concomitant distant metastases and died of their disease in a median interval of 2 (0.5–34.5) months from the last locoregional recurrence/progression.

The three patients with multiple recurrences without distant metastases were treated with surgical excision in all cases (3/3, 100%) for both the second and third progressions/recurrences. Radiotherapy was also given in 1/3 of patients (33.3%), and chemotherapy was administered in 1/3 of cases (33.3%) for the second and third progression/recurrence, respectively. Median survival was 70.3 (68.5–72) months for these patients. Additional data concerning the management and outcomes of locoregional progressions/recurrences are reported in Tables 2 and 3.

Table 1. Data at the time of diagnosis and initial management

	Distant metastatic disease subgroup (n = 52)	Locoregional progressive/ recurrent subgroup (n = 21)
Age (years)	50 (26–82)	45 (18–82)
Brest tumor laterality		
Right	28/50 (56.0)	11/21 (52.4)
Left	22/50 (44.0)	10/21 (47.6)
Bilateral	-	-
Tumor size (mm)	100 (22–430)	90 (30–300)
Skin invasion	10/46 (21.7)	4/20 (20.0)
Thoracic wall invasion	9/46 (19.6)	2/20 (10.0)
Locoregional lymph node involvement	4/52 (7.7)	1/21 (4.8)
Axillary	4/52 (7.7)	1/21 (4.8)
Internal mammary	-	-
Breast surgery		
Mastectomy	41/48 (85.4)	13/21 (61.9)[b]
Lumpectomy	6/48 (12.5)	8/21 (38.1)[a]
ALND	14/48 (29.2)	4/21 (19.0)
None	1/48 (2.1)	-
Surgical margins		
Not involved	26/30 (86.7)	7/10 (70.0)
<1 cm	5/30 (16.7)	4/10 (40.0)
>1 cm	2/30 (6.7)	-
Involved	4/30 (13.3)	3/10 (30.0)
Histological characteristics	19/52 (36.5)	6/21 (28.6)
Marked stromal growth, marked stromal cellularity, >5 mitoses per 10 high-power field and/or necrosis	16/19 (84.2)	6/6 (100.0)
Heterologous elements		
Osteosarcomatous	5/19 (26.3)	-
Chondrosarcomatous	5/19 (26.3)	1/6 (16.7)
Angiosarcomatous	3/19 (15.8)	-
Fibrosarcomatous	3/19 (15.8)	-
Distant metastases at diagnosis	13/52 (25.0)	-
Localization		
Lung	11/13 (84.6)	-
Liver	1/13 (7.7)	-
Brain	1/13 (7.7)	-
Soft tissues lumbar region	1/13 (7.7)	-
Abdominal wall	1/13 (7.7)	-
Adjuvant treatment		

Table 1. Continued

Metastases surgical excision	2/13 (15.4)	-
Chemotherapy	6/13 (46.2)	-
Indicated, but refused	1/13 (7.7)	-
Radiotherapy	1/13 (7.7)	-
Indicated, but refused	-	-
Combined chemotherapy and radiotherapy	1/13 (7.7)	-
No (neo)adjuvant oncological treatment	6/13 (46.2)	-
No distant metastases at diagnosis	39/52 (75.0)	
Chemotherapy	1/39 (2.6)	2/21 (9.5)
Indicated, but refused	-	-
Radiotherapy	9/39 (23.1)	3/21 (14.3)
Indicated, but refused	2/39 (5.1)	1/21 (4.8)
Combined chemotherapy and radiotherapy	-	-
No (neo)adjuvant oncological treatment	28/39 (71.8)	16/21 (76.2)

ALND: axillary lymph node dissection; [a]: p-value <0.05, the difference is statistically significant compared with the distant metastatic disease subgroup; [b]: p-value is 0.538, the difference is not statistically significant compared with the distant metastatic disease subgroup

Management in Metastatic MPTs

Distant metastases were observed at the time of diagnosis in 13 patients. They were localized in the lungs (11/13, 84.6%), liver (1/13, 7.7%), brain (1/13, 7.7%), soft tissues in the lumbar region (1/13, 7.7%), and in the abdominal wall (1/13, 7.7%). Subsequent progressions/recurrences in other locations were observed in six cases (6/13, 46.2%) within a median interval of 2.0 (1.0–9.0) months. Lesions were observed in bones (1/13, 7.7%), brain (2/13, 15.4%), mediastinal lymph nodes (1/13, 7.7%), adrenal glands (1/13 7.7%), and in the oral cavity (2/13, 15.4%). Distant metastatic progressions/recurrences were observed in 39 patients within 9.0 (1.0–60.0) months from the initial diagnosis of locoregionally-confined disease. Metastases were more frequently observed in the lungs (29/39, 74.4%), the bones (10/39, 25.6%), and the brain (7/39, 17.9%). Data concerning all metastases localizations are summarized in Table 2.

Patients with distant metastases at the time of diagnosis received breast surgery in all cases but one (12/13, 92.3%), who was deemed a non-surgical candidate, given multiple sites of metastases and no local pain or open wounds (38). Operated patients received a mastectomy in all the cases reporting the type of surgery, with associated axillary lymph node dissection in 5/12 cases (41.7%). Distant metastases were surgically excised in two patients (2/13, 15.4%) through partial pulmonary thoracoscopic resection (1/13, 7.7%) and cerebral metastatic excision (1/13, 7.7%). Systemic chemotherapy was administered in 6/13 cases (46.2%) and was proposed but refused by the patient in one additional case (1/13, 7.7%). Chemotherapy was administered as adjuvant treatment in all cases but one (1/13, 7.7%), in which neoadjuvant paclitaxel was given before mastectomy (35). A combination of systemic chemotherapy and radiotherapy of the chest wall was reported in one case (1/13, 7.7%) (49).

Table 2. Data concerning recurrences/progressions

	Distant metastatic disease subgroup (n = 52)	Locoregional progressive/ recurrent subgroup (n = 21)
Locoregional progression/recurrence		
1st progression/recurrence	18/52 (34.6)	21/21 (100.0)
Interval diagnosis – progression/recurrence (months)	4.0 (1.0–77.0)	4.0 (1.0–36.0)
Surgical excision	14/18 (77.8)	21/21 (100.0)
Chemotherapy	5/18 (27.8)	2/21 (9.5)
Radiotherapy	9/18 (50.0)	8/21 (38.1)
Combined chemotherapy and radiotherapy	3/18 (16.7)	2/21 (9.5)
2nd progression/recurrence	4/52 (7.7)	3/21 (14.3)+
Interval diagnosis – progression/recurrence (months)	5.0 (1.5–10.0)	21 (11–31)
Surgical excision	1/4 (25.0)	3/3 (100)
Chemotherapy	-	-
Radiotherapy	-	1/3 (33.3)
Combined chemotherapy and radiotherapy	-	-
3rd progression/recurrence	-	3/21 (14.3)+
Interval diagnosis – progression/recurrence (months)	-	25.8 (12.5–39)
Surgical excision	-	3/3 (100)
Chemotherapy	-	1/3 (33.3)
Radiotherapy	-	-
Combined chemotherapy and radiotherapy	-	-
Distant metastatic progression/ recurrence*	45/52 (86.5)	9/21 (42.9)
Interval diagnosis – progression/recurrence (months)	11.0 (1.0–60.0)	8.0 (1.5–78)
Localization		
Lungs	29/52 (55.8)	6/21 (28.6)
Bones	11/52 (21.2)	4/21 (19.0)
Brain	9/52 (17.3)	3/21 (14.3)
Heart	5/52 (9.6)	1/21 (4.8)
Oral cavity (mandibular region, tonsil)	5/52 (9.6)	-
Liver	4/52 (7.7)	-
Pancreas	3/52 (5.8)	-
Bowel	3/52 (5.8)	-
Kidney	2/52 (3.8)	-
Pleural cavity	2/52 (3.8)	-

Table 2. Continued

Mediastinal lymph nodes	2/52 (3.8)	1/21 (4.8)
Stomach	2/52 (3.8)	-
Skin	2/52 (3.8)	-
Thyroid gland	1/52 (1.9)	-
Adrenal glands	1/52 (1.9)	-
Parotid gland	1/52 (1.9)	-
Subphrenic space	1/52 (1.9)	-
Intraperitoneal	1/52 (1.9)	-
Supraclavicular lymph nodes	-	-
Supraclavicular lymph nodes	-	1/21 (4.8)
Treatment		
Metastases surgical excision	16/45 (35.6)	6/9 (66.7)
Chemotherapy	28/45 (62.2)	4/9 (44.4)
Indicated but refused	6/45 (13.3)	-
Radiotherapy	15/45 (33.3)	1/9 (11.1)
Indicated, but refused	2/45 (4.4)	-
Combined chemotherapy and radiotherapy	14/45 (31.1)	-
No metastases treatment	7/45 (15.6)	1/9 (11.1)

⁺: Only patients with locoregional progressions/recurrences in the absence of distant metastases were analyzed; *: For patients with distant metastases at the time of diagnosis, other localization than initially observed metastases

Metastatic progressions/recurrences in patients with no distant lesions at diagnosis were treated through metastases surgical excision in 13/39 cases (33.3%), which in most cases represented partial pulmonary resections (6/39, 15.4%). Excisions of bowel, kidney, adrenal gland, and heart metastases were also reported. Chemotherapy was proposed in 32/39 cases (82.1%), administered in 26/39 cases (66.7%), and refused by 6/39 patients (15.4%). Combined radiotherapy was reported in 12/39 cases (30.8%), which was mainly used to irradiate the chest wall and axilla for concomitant locoregional progressions/recurrences (6/39, 15.4%). However, radiotherapy was also reported for irradiation of scalp, pancreatic, bone, and parotid metastases. Additional data concerning the management and outcomes of metastatic MPT are reported in Tables 2 and 3.

Overall, metastatic MPTs were managed through surgical excision, chemotherapy, radiotherapy, or a combination of these three in 84.6% of cases, and chemotherapy was proposed in 75.0% of cases. In 15.4% of cases, patients received no oncological treatments. Reasons for this decision, such as patient refusal, poor general conditions, and no expected benefits, were rarely reported.

Chemotherapeutic Agents

The type of chemotherapeutic agents used was reported in 32/38 cases (84.2%), and details concerning dosages, intervals, and the number of cycles were reported in 9/38 patients (23.7%). The most frequently used chemotherapeutic agents were doxorubicin and ifosfamide (14/38, 36.8%). Protocols comprised 6-8 cycles with doxorubicin 25 or 30 mg/m^2 days 1-2, and ifosfamide 2 or 7.5 g/m^2 days 1–5. Other chemotherapeutic agent combinations were only reported in one or two cases and comprised a vast heterogeneity of treatments summarized in Table 4. No differences were observed in survival between patients who received different chemotherapeutic agents. Chemotherapy was always administered as adjuvant treatment, except in two cases where chemotherapy was given before breast surgery (35, 45). Chemotherapeutic agents were always administered systemically, except in one case where epirubicin was injected as chemoembolization for breast mass reduction (62).

Table 3. Follow-up and Outcomes

	Distant metastatic disease subgroup (n = 52)	Locoregional progressive/recurrent subgroup (n = 21)
Follow-up		
Total time (months)	14.5 (2.0–152.0)	13.0 (2.5–98.5)
Status at last control		2/21 (9.5)
NED	-	12/21 (57.1)
AWD	18/51 (35.3)	9/21 (42.9)
DOD	33/51 (64.7)	72 (2.5–98.5)
Survival time (months)	24 (2–152)	9/15 (60.0)
2-year survival rate	19/39 (48.7)	6/12 (50.0)
5-year survival rate	7/33 (21.2)	

NED: no evidence of disease; AWD: alive with disease; DOD: died of disease

Radiotherapy

Radiotherapy was used to treat locoregional as well as distant progressions/recurrences. Information concerning the location, doses, and fractions was reported in 13/38 cases (34.2%). Locoregional radiotherapy on the remaining breast and/or chest wall was administered with a median dose of 60 (50–84) Gray and a median number of fractions of 28 (10–30). Locoregional radiotherapy was administered as adjuvant treatment following local excisions in all cases except one, in which neoadjuvant radiotherapy was administered before the excision of the lesion (33). Details concerning radiotherapy in other localization were only reported for single disparate cases and are not reported.

Long-Term Outcomes

In the DMD subgroup, data concerning outcomes were available in 51/52 patients (98.1%), and the median follow-up was 14.5 (2.0–152.0) months. At the last control, 18/51 patients (35.3%) were alive with the disease, and 33/51 (64.7%) died of the disease. The median survival time was 24.0 (2.0–152.0) months. The 2-year and 5-year survival rates were 48.7% and 21.2%, respectively.

In the LRPR subgroup, data were available in all patients, and the median follow-up was 13.0 (2.5–98.5) months. At last control, 8/21 patients (38.1%) presented with no evidence of disease, 4/21 patients (19.0%) were alive with the disease, and 9/21 (42.9%) died of the disease. The median survival time was 72.0 (2.5–98.5) months. The 2-year and 5-year survival rates were 60.0% and 50.0%, respectively. Patients in the LRPR subgroup who presented subsequent distant metastatic lesions had a 2-year and 5-year survival rate of 27.3% and 18.2%, respectively.

Table 4. Chemotherapeutic agents

	Distant metastatic disease subgroup (n = 52)	Locoregional progressive/ recurrent subgroup (n = 21)
1st line chemotherapy		
Doxorubicin and Ifosfamide	8/52 (15.4)	3/21 (14.3)
Doxorubicin, Ifosfamide and Dacarbazine	1/52 (1.9)	-
Doxorubicin and Cyclophosphamide	2/52 (3.8)	-
Doxorubicin and Bevacizumab	-	1/21 (4.8)
Epirubicin and Cyclophosphamide	1/52 (1.9)	-
Epirubicin, Cyclophosphamide and Fluorouracil	1/52 (1.9)	-
Liposomal Doxorubicin, Cisplatin and Paclitaxel	1/52 (1.9)	-
Paclitaxel	1/52 (1.9)	-
Gemcitabine and Docetaxel	1/52 (1.9)	-
Ifosfamide	-	-
Apatinib	-	-
2nd and 3rd line chemotherapy		
Doxorubicin and Ifosfamide	3/52 (5.8)	-
Paclitaxel and Bevacizumab	2/52 (3.8)	-
Pazopanib	2/52 (3.8)	-
Bevacizumab and Temzolomide	1/52 (1.9)	-
Doxorubicin and Cyclophosphamide	1/52 (1.9)	-
Gemcitabine and Carboplatin	1/52 (1.9)	-
Gemcitabine and Docetaxel	1/52 (1.9)	-
Gemcitabine and Taxotere	-	1/21 (4.8)
Docetaxel	1/52 (1.9)	-
Paclitaxel	1/52 (1.9)	-
Apatinib	1/52 (1.9)	-
Ifosfamide	1/52 (1.9)	1/21 (4.8)

The 5-year survival rate in the DMD subgroup was lower than the LRPR subgroup, although not significant (21.2% vs. 50.0%, p = 0.07). Comparisons concerning survival time and the 2-year survival rate between subgroups were not significant.

No survival differences were observed between patients managed with different therapeutic strategies in either subgroup. Data concerning outcomes are summarized in Table 3, and Kaplan-Meier survival curves are presented in Figure 2.

Discussion and Conclusion

MPTs of the breast constitute an uncommon condition and represent 0.03–0.3% of all breast cancers, with an annual incidence of about 2/1,000,000 (1). Surgery is the management of choice for the primary treatment of localized MPTs. However, due to its rarity, little is known about appropriate management in the case of metastatic or locally recurrent MPTs. In this study, we systematically reviewed all cases of metastatic and/or recurrent MPTs published in the last 10 years to give an overall view of their current management and outcomes.

The national cancer center network (NCCN) recommends treating primary MPTs with lumpectomy or mastectomy in cases of impossibility to adequately obtain 1 cm margins or for cosmetic reasons (67). Mastectomy did not prove superior to wide excision in terms of survival and, therefore, should not be routinely performed (68). Nodal involvement is very rare, and sentinel lymph node biopsy or axillary lymph node dissection are not indicated unless there is suspicion of lymph nodal metastases (67, 69). Adjuvant radiotherapy, chemotherapy, and hormonotherapy are not recommended for the primary treatment of localized MPTs (67).

Locoregional recurrences are common complications of MPTs and are observed in about 12–65% of cases (70, 71). In this systematic review locoregional recurrences were observed within a median time of 8.9 (1.0–36.0) months (70, 71). Positive surgical margins and large tumor size seem to be the main risk factors for locoregional recurrences (70, 72). In this review, these characteristics were found in about 2/3 of patients presenting with a locoregional recurrence.

Although adjuvant radiotherapy following primary surgery is not routinely indicated, in the case of locoregional recurrence, the NCCN recommends considering local irradiation following tumor excision (67). Adjuvant radiotherapy following primary surgery seems to reduce locoregional relapses but with no proven effect on overall survival, regardless of the surgical margin status (73-77). The role and impact of adjuvant radiotherapy for locoregional relapses are unclear due to limited evidence. In our review, 100% of tumor recurrences were surgically excised, while adjuvant radiotherapy was administered in just over a third of cases. Our review showed no survival differences in locoregional relapsing patients treated with or without adjuvant radiotherapy. No validated guidelines exist for radiation treatment for recurrent MPTs, and in our review, radiotherapy modalities were rarely reported, and no general agreement was found. Combined radio- and chemotherapy seem not indicated and have been reported only twice (22, 61). Multiple recurrences were rarely reported, and except for surgical excision, no consistent trends were observed in their adjuvant treatment. Surgical excision of the local lesion at each relapse seems appropriate (39), associated with a single course of radiotherapy. However, the role of adjuvant chemotherapy for multiple local recurrences is unclear and currently not indicated unless concomitant distant metastases are observed.

As previously observed (70), we found locoregional recurrence to be a strong predictor of distant metastases, with 42.9% of patients developing distant disease after a median time of 2.0 (0.5–14.0) months from their first locoregional recurrence. Yet, the relationship between local relapses and distant metastatic spread is unclear and often debated by authors (78). In our review, survival in patients with locoregional recurrent MPTs was similar to the reported overall survival in the case of MPTs (2, 70, 78, 79). However, the observed 5-year survival rate of 50.0% reduced dramatically to 18.2% in those patients who subsequently developed distant metastases. This highlights the relative controllability of localized MPTs and their locoregional recurrences but the difficulty in managing a distant metastatic spread.

Around 1.5% of MPTs present with metastatic disease at diagnosis, and 10–25% are associated with distant metastatic recurrences, with predominant hematogenous spread and lesions observed in nearly all

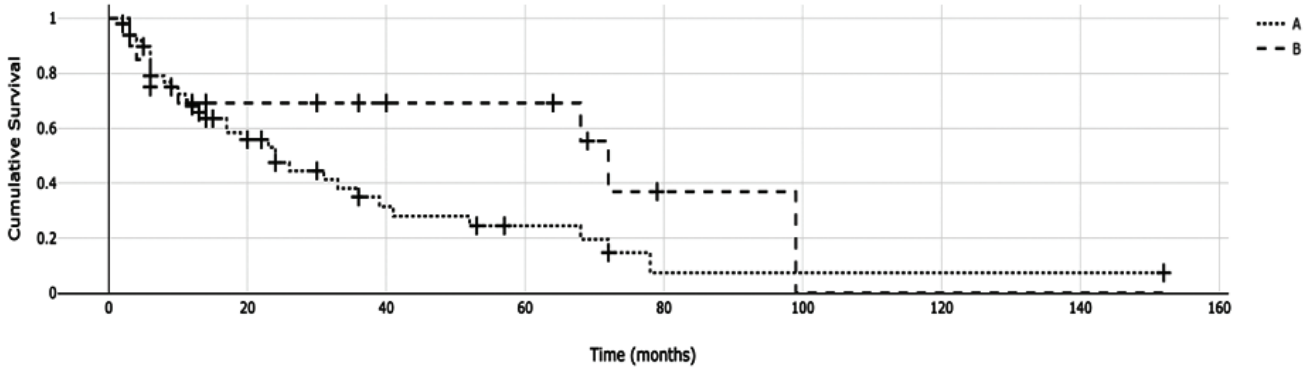

Figure 2. Kaplan-Meier survival curves

A: distant metastatic disease subgroup; B: locoregional progressive/recurrent subgroup

organs but predominantly in lungs and bones (1, 70, 79-82). In our review, metastatic recurrences were observed within a median time of 9.0 (1.0–60.0) months. Similar to other studies, the intervals between primary treatment and metastatic recurrences vary widely, from a few weeks to several years (70, 71). The main risk factors associated with the development of distant disease are large tumor size, infiltrative surgical margins, marked stromal overgrowth or cellularity, >5 mitoses per 10 high-power fields, and tumor necrosis (70, 79). In our study, these features were observed in about 3/4 of patients presenting with distant metastases. The presence of heterologous sarcomatous elements could predispose to the development of distant metastases (83), but this association was not universally shared (78). In our study, patients with metastatic recurrences presented with osteosarcomatous and/or chondrosarcomatous heterologous elements in about 70% of cases. However, the small sample size limits any possible suggestions of the relation between these histological features and metastatic MPTs. Patients with metastatic disease, whether at diagnosis or for relapses, should be treated in accordance with the guidelines for metastatic soft tissue sarcomas, as recommended by the NCCN (67). However, these patients frequently do not respond to chemotherapy and often have poor survival (84). In our review, chemotherapy was proposed in around 3/4 of cases with distant metastases, and a wide range of chemotherapy regimens was administered. Anthracycline and alkylating agent-based combination regimens were most frequently administered, and the combination of doxorubicin-ifosfamide was administered in more than one-third of cases. Protocols varied between 6–8 cycles with doxorubicin 25 or 30 mg/m^2 days 1-2, and ifosfamide 2 or 7.5 g/m^2. Due to limited data, there was no superiority in a specific treatment regimen over the others, as reported in earlier studies. Currently, there are no randomized clinical trials assessing the role of adjuvant chemotherapy in MPTs, and its role remains undefined (78, 79, 82). This uncertainty was highlighted by the fact that, in our review, more than 1/3 of patients with distant metastases were not offered or considered for chemotherapy. In part of these cases, metastases were managed through surgical excision and/or radiotherapy, but more than 20% of patients received no oncological treatments.

Overall, patients with MPTs have a 5-year survival rate of around 65% (2, 70, 78, 79), which, from our results, reduces to approximately 20% in case of metastatic disease. Conversely, patients with localized disease present a 10-year survival rate as high as 90% (85). In addition to distant metastases, survival seems to be affected by the tumor size, the surgical margin status, the stromal overgrowth and differentiation, and the presence of osteosarcomatous or chondrosarcomatous histological features (70, 86-89). Due to the limited sample size, we could not assess these features in this review. Characteristics predisposing to locoregional relapses, metastatic disease, and poor prognosis should be studied carefully in future research to identify possible indications for primary adjuvant chemo- and/or radiotherapy. In addition, due to the relative uncertainty and confusion around the optimal management of MPTs, more specific international and local guidelines for the management of MPTs are needed.

The main limitation of this study was its small sample size. In addition, analyzed data were extrapolated from case reports and small case series, which were rarely oriented toward metastatic or recurrent MPT, and which frequently reported only limited and incomplete data. This may have resulted in selection and information bias. However, to our knowledge, this study represents the only review of metastatic or recurrent MPT and could improve the general knowledge about the current trends in managing this rare condition.

Clinical and Research Consequences

Due to limited data and inconsistent results, this study carries no clinical consequences. However, we see an urgent need to create international registers and perform specific trials to improve evidence about treatment strategies for recurrent or metastatic MPTs of the breast.

Management of recurrent and metastatic MPTs is a challenge. Surgery remains the fundamental approach, but the role of adjuvant radio- and chemotherapy remains controversial due to the lack of evidence of their positive impact on survival. This study reports the current trends in managing MPTs, confirming inconsistent approaches and a lack of evidence supporting the superiority of one or some treatment options. Further trials and international registers are needed to gather evidence about treatment options, therapy response, and patient-reported outcomes to implement new management strategies.

Ethics Committee Approval: No local review board approval was needed for this research project (CER-VD, Lausanne, Switzerland).

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Authorship Contributions

Concept: Y.H., D.H.; Design: Y.H., D.H.; Data Collection and/or Processing: E.S., Y.H.; Analysis and/or Interpretation: E.S., Y.H., D.H.; Literature Searching: E.S., Y.H.; Writing: E.S., Y.H.

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Original Article

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Current Challenges and Perspectives in Breast Cancer in Elderly Women: The Senologic International Society (SIS) Survey

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ABSTRACT

Objective: Mammographic screening and management of breast cancer (BC) in elderly women are controversial and continue to be an important health problem. To investigate, through members of the Senologic International Society (SIS), the current global practices in BC in elderly women, highlighting topics of debate and suggesting perspectives.

Materials and Methods: The questionnaire was sent to the SIS network and included 55 questions on definitions of an elderly woman, BC epidemiology, screening, clinical and pathological characteristics, therapeutic management in elderly women, onco-geriatric assessment and perspectives.

Results: Twenty-eight respondents from 21 countries and six continents, representing a population of 2.86 billion, completed and submitted the survey. Most respondents considered women 70 years and older to be elderly. In most countries, BC was often diagnosed at an advanced stage compared to younger women, and age-related mortality was high. For this reason, participants recommended that personalized screening be continued in elderly women with a long life expectancy.

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In addition, this survey highlighted that geriatric frailty assessment tools and comprehensive geriatric evaluations needed to be used more and should be developed to avoid undertreatment. Similarly, multidisciplinary meetings dedicated to elderly women with BC should be encouraged to avoid under- and over-treatment and to increase their participation in clinical trials.

Conclusion: Due to increased life expectancy, BC in elderly women will become a more important field in public health. Therefore, screening, personalized treatment, and comprehensive geriatric assessment should be the cornerstones of future practice to avoid the current excess of age-related mortality. This survey described, through members of the SIS, a global picture of current international practices in BC in elderly women.

Keywords: Breast cancer; elderly women; screening; treatment; international survey; senologic international society

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Key Points

- Breast cancer
- Elderly women
- Screening
- Treatment
- International survey
- Senologic international society

Introduction

Breast cancer in elderly women is a major public health issue. Age is one of the main risk factors for developing breast cancer and in the coming years, the life expectancy of women will increase worldwide. According to Globocan 2020 data, 20% of breast cancers and 50% of breast cancer deaths are seen in women over 70 years of age (1). Indeed, in 2020 estimated incidence and mortality in women aged ≥70 years were 194.1 and 87.8/100,000, respectively. According to estimates for 2040, breast cancer incidence and mortality are expected to almost double in women aged 70 years and over (+93.4% and +95.2%, respectively) (2). Compared to women aged up to 69 years-old (+26.0% and +28.4%), these increases in incidence and mortality are almost four-fold higher. There is therefore an urgent need to improve breast cancer prevention, screening and management in this elderly population.

Defining precisely what an elderly woman is may be difficult, as reflected by the divergence in the experts' responses and the current literature. According to the World Health Organization, a person is old from the age of 60 years, which is limited to the sole notion of chronological age. The elderly population is highly heterogeneous and the notions of frailty, poly pathology and poly medication must be taken into account, along with chronologic age.

The clinical and pathological characteristics of breast cancer in elderly women are different from those of breast cancer in younger women (3). Moreover, management of breast cancer differs in elderly patients due to a great heterogeneity in this population because of increased frailty, comorbidities, multiple medications, and so on. It is no longer only chronological age that is taken into account when evaluating these patients, but also biological age. In 2007, the International Society of Geriatric Oncology (SIOG) published the first guidelines on the management of breast cancer in elderly individuals (4). In 2012, these guidelines were then updated jointly with the European Society of Breast Cancer Specialists (EUSOMA) (5). Current guidelines were published in 2021 by EUSOMA and SIOG (6). Yet, there are still many unresolved questions in the management of these patients.

The international Society of Senology (SIS) is dedicated to promoting breast health and improving the care of breast cancer patients, taking into consideration, medical, social, economic and ethical constraints.

The objective of this survey was to investigate, through members of the SIS, current international practices in breast cancer in elderly women worldwide, highlighting topics of debate and suggesting perspectives.

Materials and Methods

Members of the SIS network were asked to participate in an online survey with a Microsoft® Forms questionnaire (Microsoft Inc., Redmond, WA, USA). Between the 28th of June 2022 and the 25th of August 2022, participants were invited to answer the questionnaire via email. The answers were directly recorded into an online database and only one response per participant was allowed, but more than one response was allowed from the same country, because of regional disparities in any single country. Some questions were multiple choice, others were open-ended.

The online survey consisted of 55 questions. Section 1 (6 questions) was about the respondent themselves, such as affiliation and medical specialty. Section 2 (5 questions) was about breast cancer epidemiology in the participant's country (incidence, mortality, mean age concerned all BC, general life expectancy). Participants were asked about breast cancer screening in Section 2 (11 questions), including the existence of a national breast cancer screening program, and if one was present, details about the organization of breast cancer screening: beginning and ending age, frequency of screening, tests used for screening, number of mammogram readers, start date of screening, participation rate, and methods for financing this screeining. Section

3 (11 questions) concerned elderly women with breast cancer and asked about definition of an elderly woman, breast cancer risk and aggressiveness and diagnosis (average stage at diagnosis, lymph node involvement, breast cancer screening efficacy, risk of overdiagnosis). Section 5 (13 questions) was about therapeutic management of elderly women with breast cancer and enquired about topics such as onco-geriatric evaluation, surgical concerns, medical treatment specifications in elderly women, use of radiotherapy, and therapeutic abstention. Finally, in Section 6 (9 questions) respondents were asked about future perspectives concerning screening, diagnosis and therapeutical management of elderly women with breast cancer. The full questionnaire is available as as Supplementary Material.

Statistical Analysis

Statistical analysis was conducted with R version 4.1.3 (2022-03-10) (7). For discrete variables, we performed a two-sided χ^2 tests (or Fisher's Exact tests) was performed. For continuous variables, Wilcoxon tests were used. Correlation tests were made using Pearson's method. The data (life expectancy in the participant's country and the age threshold) were distributed normally according to the Shapiro-Wilk tests (0.3523 and 0.291 respectively).

Results

Twenty-nine completed questionnaires were returned, from 28 participants (one double response). Participants came from 21 different countries on six continents: Algeria, Argentina, Australia, Brazil, Cameroon, China, Croatia, France, Germany, Greece, Israel, Japan, Kenya, Lithuania, Nepal, Nigeria, Poland, Saudi Arabia, Senegal, Turkey and the United States (Figure 1). These countries represent about 2.86 billion people, among whom 340 million people were over the age of 70 years. Participants were mostly surgeons specializing in breast cancer (78.5%, n = 22), while others were radiologists (7.1%, n = 2), oncologists (7.1%, n = 2), a nuclear medicine doctor (3.6%, n = 1) and one unspecified (3.6%, n = 1). Some of the survey results are reported in Tables 1 and 2. The median completion time for the questionnaire was 32 minutes per participant.

Definition of An Elderly Woman

Half of the participants identified women aged 70 years and over as elderly (n = 14, 50%). Other ages used as a cut-off for definition of an elderly woman were: 65 years for 17.9% (n = 5), 75 years for 10.7% (n = 3), 69 years for 3.6% (n = 1), 60 years for 7.1% (n = 2), 55 years for 3.6% (n = 1), and 50 years for 3.6% (n = 1). No significant correlation was found between life expectancy in the participant's country and the age threshold (p = 0.232). Two participants took into account comorbidities for the definition of elderly.

Breast Cancer Screening and Diagnosis

Thirteen (62%) participating countries reported the existence of a breast cancer screening program, the other eight countries (38%) did not. Countries with a breast cancer screening program represented approximately 1.1 billion women worldwide. Among countries with breast cancer screening programmes, 11 had at least a high Inequality-adjusted Human Development Index (Ia-HDI), while the majority of countries without high HDI did not have breast cancer screening (75%). High Ia-HDI was significantly associated with the presence of breast cancer screening (p = 0.0233). Moreover, the presence of a breast cancer screening program was significantly associated with breast cancer mortality reduction in terms of age-standardized rates and lower mortality (13.7 versus 17.6 deaths/100,000, p = 0.030). In the countries where a screening program was applied, the ages in years at which screening ended were: 69 [35.3% (n = 6)]; 74 [23.5% (n = 4)]; 75 [17.6% (n = 3)]; and 80 [9.8% (n = 2)]. In Japan alone, there was no age limit on the screening program at which screening would be terminated. The upper age limit for screening was significantly correlated with life expectancy (r = 0.688, p = 0.013), as higher life expectancy was associated with a later ending age for screening.

Breast cancer screening involved mammographies in all countries (100%, n = 17), clinical examination in 64.7% (n = 11), breast ultrasound in 47.1% (n = 8) countries, and two participants also used tomosynthesis (11.8%), although the screening recommendations for their country's did not mention this technique. In the majority of countries, screening was recommended every two years (88.2%, n = 15), whereas in two countries (China and the United States), it was performed yearly in some parts of these countries. Mammographies were read by two radiologists in 76.5% of cases (n = 13), and by one radiologist (n = 4) otherwise. Reported participation rates (n = 15) were variable from one country to another, ranging from 15% (some China regions) to 80% (Some statesof the USA), with an average of 53.4%. Screening was fully reimbursed in 70.6% of cases (n = 12), partially reimbursed in 23.5% of cases (n = 4), and at the patient's expense in 5.9% of cases (n = 1). The invitation methods also varied

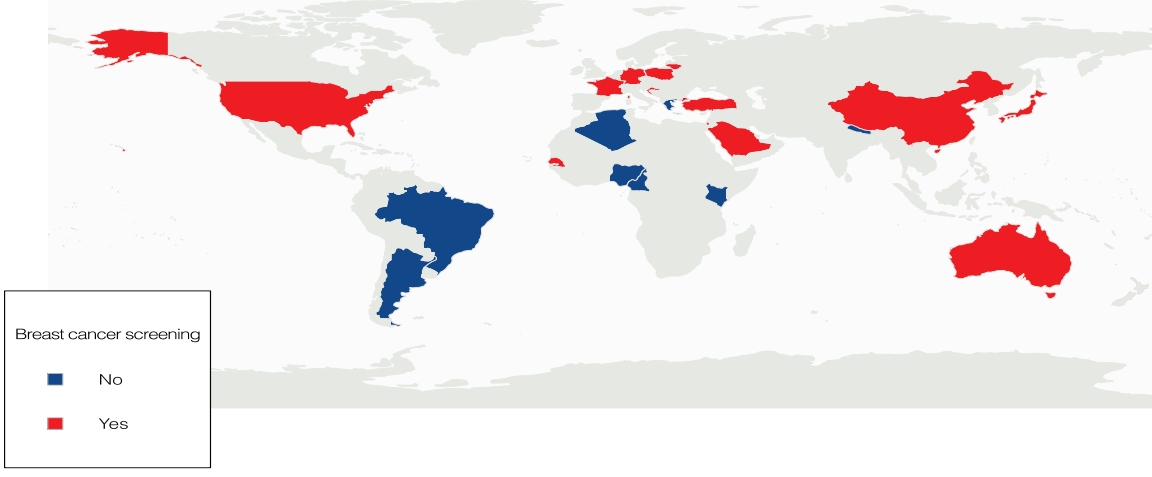

Figure 1. World map of participants' countries, according to a national breast cancer screening program presence

Table 1. Participants' responses: Breast cancer screening and diagnosis in elderly women

Question	Result	
	n/Mean	%
Is there a national breast cancer screening program in your country? (n = 28)		
Yes	17	61
No	11	39
Which tests are performed? (n = 17)		
Mammography	17	100
Clinical examination	10	59
Breast utrasound	8	47
Tomography	2	12
How often? (n = 17)		
Every 2 years	15	88
Yearly	2	12
How many radiologists read the mammograms? (n = 17)		
Two	14	82
One	3	18
How is it financed? (n = 17)		
Total reimbursement	12	71
Partial reimbursement	4	24
Participant expense	1	6
Are older patients diagnosed at a more advanced stage of the disease compared to younger patients? (n = 28)		
Yes	15	54
No	8	29
Maybe	5	18
Are elderly women included in breast cancer screening in your country? (n = 28)		
No	14	50
Yes, individual screening	7	25
Yes, organized screening program	5	18
Other	2	7
Is breast cancer screening more effective in elderly women? (n = 28) (i.e., are there fewer false negatives)		
Yes	17	61
No	6	21
Maybe	5	18
Are there less unnecessary biopsies? (n = 28) (i.e., are there fewer false positives)		
Yes	19	68
No	7	25
Maybe	2	7
Are there less benign diseases in elderly women? (n = 28)		
Yes	19	68
No	7	25
Maybe	2	7
Are there less interval cancers in elderly women? (n = 28)		
Yes	11	39
No	9	32
Maybe	8	29

from one country to another: telephone, mail, via the attending physician or the employer, other or none.

Concerning breast cancer screening in elderly women, 48% of participants reported that older women were not included in screening programs, while 21% offered individual screening, and 17% of respondents reported that elderly women were included in organized screening programs. In the remaining cases, it depended on the program. Of interest, the majority of participants answered that the diagnosis of breast cancer in elderly women was done at a more advanced stage (51.7%), and screening was more effective in older women (i.e., fewer false negatives, 59%). Elderly women had less unnecessary breast biopsies (i.e., fewer false positives, 66%). Forty-one percent and 35% (n = 10) of the participants answered that there were fewer interval cancers, and less overdiagnosis, respectively. These results may be related to the good performances of mammography in detecting tumors (lower breast density in older women allowing easier reading).

Breast Cancer Management in Elderly Women

Only 14% of participants systematically used a geriatric assessment tool in their routine practice for their patients. Others reported its use sometimes for 59%, and never for 28%. Onco-geriatric consultation was systematically offered by 21% of respondents (48% sometimes, and 31% never). Specialists offered this specific consultation in women with multiple and severe comorbidities, sometimes even in all cases depending on the age (starting at 65 years of age with comorbidities for some, or 80 years of age and older for others). Some specialists also requested geriatrician consultation for treatment decisions and the risk of treatment complications.

Regarding the use of mastectomy for older women, participants' responses were heterogeneous: 33% perfomed more, 33% the same rate and 33% less of this intervention compared to younger women. For 90% of participants, being elderly was not a contra-indication for oncoplastic surgery. Breast reconstruction was not contra-indicated in elderly women for 59% of participants, 7% answered that all techniques were contra-indicated, and 34% were undecided. Sentinel lymph node biopsy indications and axillary lymph node dissection indications were not different in elderly women for the vast majority of participants (respectively 79% and 76%).

Concerning adjuvant treatments, 79% of participants applied adjusted protocols for chemotherapy, 77% performed less neoadjuvants protocols and 76% had adjusted protocols for radiotherapy. Exclusive hormone therapy was generally prefered for hormone receptor-positive breast cancer patients with severe comorbidities, or contra-indicated for chemotherapy or/and radiotherapy. Some participants chose therapeutic abstention for patients with multiple and severe comorbidities, frail patients with short life expectancy, or in case of multiple metastases, or triple negative tumors in elderly patients with poor performance status. One participant also answered that this was the case in small DCIS or low grade tumors in patients with short life expectancy.

Table 2. Participants' responses: Treatment and future perspectives

	Question	Result	
		n/Mean	%
Elderly women and breast cancer management	**Do you use a geriatric assessment tool in your routine practice?** (n = 28)		
	Sometimes	16	57
	Never	8	29
	Always	4	14
	Do you offer a specialised oncogeriatric consultation to elderly women with breast cancer? (n = 28)		
	Sometimes	13	46
	Never	9	32
	Always	6	21
	Do you perform more or less mastectomies in elderly women? (n = 28)		
	Less	10	36
	Equally	10	36
	More	9	32
	Are elderly women contra-indicated for oncoplastic surgery? (n = 28)		
	No	25	89
	Yes	3	11
	Is breast reconstruction contra-indicated in elderly women? (n = 28)		
	No	17	61
	Yes, some techniques	9	32
	Yes, all techniques	2	7
	Are sentinel lymph node biopsy indications different in elderly women? (n = 28)		
	No	22	79
	Yes	6	21
	Are axillary lymph node dissection indications different in elderly women? (n = 28)		
	No	21	75
	Yes	7	25
	How is adjuvant chemotherapy performed in elderly women? (n = 28)		
	Adjusted protocols	23	82
	Same protocols as younger patients	4	14
	Other situations	1	4
	Is neoadjuvant chemotherapy more or less performed in elderly women? (n = 28)		
	Less	22	79
	Equally	4	14
	More	2	7
	How is adjuvant radiotherapy performed in elderly women? (n = 28)		
	Adjusted protocols	22	79
	Same protocols as younger patients	4	14
	Other situations	2	7
Perspectives	**Do you offer clinical trials for elderly women with breast cancer in your center? (n = 28)**		
	No	17	61
	Yes	11	39
	Do you think breast cancer screening should be continued in elderly women? (n = 28)		
	Yes	17	61
	Maybe	10	36
	No	1	4
	Would you consider a specific multidisciplinary meeting to older women with breast cancer in order to optimize their management? (n = 28)		
	Yes	20	71
	Maybe	5	18
	No	3	11
	In your opinion, do you think that specific guidelines should be established/followed for elderly women with breast cancer? (n = 28)		
	Yes	20	71
	Maybe	7	25
	No	1	4

Perspectives

The majority (62%) of participants did not have clinical trials for elderly women with breast cancer, but conisidered that offering more clinical trials in elderly women would allow better adaptation of treatments. Concerning breast cancer screening continuation in elderly women, only one participant (3%) disagreed, because of the low percentage of elderly women in the population demography in his country. Participants in favor of continuing screening argued that age is one of the main risk factors for developing breast cancer, and that elderly women are considered to be at high risk and have a higher mortality rate. The goal of continued screening would be to detect lesions at an earlier stage, allowing a decrease in treatment morbidities and mortality to preserve quality of life (more than overall survival). Participants also noted that mammography is easily performed and simple to interpret in older women because of low breast density. The undecided participants mentioned the notion of life expectancy: for patients with a life expectancy of at least five years, some were in favor of continuing screening, and noted that more studies are needed to evaluate the efficiency and benefits of screening program in this age group.

Participant-suggested age for ending the screening program ranged from 70 to 85 years, or as long as the patient was healthy and had at least five years of life expectancy. They also suggested continuing clinical examinations and mammography screening yearly or every two years. Regarding ways to improve diagnostic management of breast cancer in elderly women, several mechanisms were suggested: integration in a population based screening program; improvement of

Table 3. Topics for which there was strong agreement and related perspectives

Topic	Strong agreement	Perspectives
Surgery	Axillary surgery indications were similar to younger women, and oncoplastic techniques were mostly not contra-indicated	Breast reconstruction and oncoplastic techniques should be more offered to elderly women, according to individual health condition and preferences
Adjuvant treatments	Adjusted chemotherapy and radiotherapy protocols should be used	Specific guidelines should be established/followed for adjusted protocols in elderly women with breast cancer
Oncogeriatric assessment	Geriatric assessment and specialized geriatric consultations are not enough used	Geriatric assessment tools and specialized geriatric consultations should be developed (including life expectancy models)
Screening	Screening's performances are better in this elderly population	Screening continuation should be encouraged in elderly women
Multidisciplinary meetings	Multidisciplinary meetings dedicated to elderly women with breast cancer are uncommon	Multidisciplinary meetings dedicated to elderly women with breast cancer should be encouraged
Clinical trials	Elderly women are often excluded from clinical trials	Elderly women should be included in clinical trials

public health awareness and self-examination methods; optimization of outpatient indications for biopsies; early referral to specialist units; and to discriminate diagnostic evaluation decisions and indications on the basis of chronological age.

To improve the therapeutic management of breast cancer in elderly women, participants emphasized the importance of early diagnosis and individualised approaches to avoid over- or under-treatment. They also encouraged a multidisciplinary approach involving several specialists, such as geriatricians, oncologists, and maybe cardiologists and psychiatrists, if necessary. Indeed, 72% of participants considered a specific multidisciplinary meeting to dicuss older women with breast cancer in order to optimize their management. Of the participants surveyed, 72% were favorable for the adoption of specific guidelines for elderly women with breast cancer.

Discussion and Conclusion

This survey produced a global picture of current international practices in breast cancer in elderly women, through members of the SIS. Of interest, these results show that while there was strong agreement in some areas, others remained heterogeneous and not consensual. This may be explained by the fact that demographic, socio-cultural, economical factors (re-imbursement for mammography can reduce screening rate) and, breast cancer awareness, knowledge, incidence and mortality are different between countries. The lack of sufficient infrastructure and the cost of nationwide mammographic screening also play a role in these differences. However, a population-based mammography screening program in a middle-income country has shown that screening is cost-effective and provided early diagnosis (8). Below, we discuss the issue of breast cancer screening among elderly women and specific questions regarding treatment, highlighted by this survey and the EUSOMA/SIOG 2021 guidelines (6). Moreover, some perspectives and possible future changes emerged from this survery.

Breast Cancer Screening in Elderly Women

The question of extending screening in elderly women is controversial: the majority of respondents favored continued screening, and only one did not agree. A review by Walter et al. (9) published in 2014 found that there is no randomized trials of screening mammography that included women over the age of 74 years, and observational data showed that in elderly women with a life expectancy ≥5-10 years it is not known whether screening decreases breast cancer mortality. The authors suggested that this choice should be made according to the individual woman's preference and health condition. Besides mortality, screening could also allow a less aggressive treatment, such as breast-conserving surgery, sentinel lymph node biopsy, less chemotherapy, and thus reduce the negative impact of treatment on quality of life.

Of interest, Vacek and Skelly (10) published a prospective study in 2015 of the use and effects of screening mammography in women aged 70 years and older. They included 20,697 women with a follow-up of 10.2 years and found that screening declined by 9% for each year of age, and advancing age was associated with more clinically-detected cancers. Interestingly, clinically-detected breast cancer was significantly associated with higher breast cancer mortality [hazard ratio (HR) = 1.68 (95% confidence interval (CI) = 1.43-1.96) for clinically-detected *versus* HR = 1.22, (95% CI = 1.07-1.40) for screening-detected], thus demonstrating a benefit of continuing screening. The authors also concluded that early treatment improved survival.

In a meta-analysis including seven studies published in 2016 by Braithwaite et al. (11) the authors showed that, apart from older women with severe comorbidity, screening may improve life expectancy in women 65 years and older (limited evidence). In 2020, Demb et al. (12) published an observational study of 222,088 women and investigated breast cancer incidence and mortality in women aged between 66 and 94 years who underwent screening and found that mortality by other causes was many times higher than breast cancer mortality. Moreover, mortality by other causes increased with advancing age and comorbidities, therefore suggesting that benefit from continued screening would decrease in these situations. Similarly, García-Albéniz et al. (13) conducted an observational study from the same database (Medicare) including 1,058,013 women aged 70 to 84 years who had a life expectancy of at least 10 years and compared two screening strategies: continuing annual mammography, and stopping screening. This result showed that continuing screening reduced the 8-year risk for breast cancer death by 1.0‰ [HR, 0.78 (CI, 0.63 to 0.95)] in women aged from 70 to 74 years. Conversely, in those aged 75 to 84 years, the corresponding HR was 1.00 (CI, 0.83 to 1.19), thus supporting the discontinuation of screening in women over 74.

The 2021 updated recommendations from the EUSOMA/SIOG (6) stated that *"screening in women ≥75 years could be appropriate with the individual decision based on risks and benefits, patient preference, physiological age, and life expectancy, but might lead to increased rates of overdiagnoses (level 4)"*. American College of Radiology (ACR) and Society of Breast Imaging (SBI) also updated breast cancer screening recommendations for all women at average risk in 2021 and stated that screening should continue after the age of 74 years without an upper age limit, unless severe comorbidities limit life expectancy (14).

Consequently, in elderly women (≥75 years and over), optimal screening should be individual, and not organized. The decision to continue or stop screening should be made on a individual basis, but it is important to note that the fact that organized screening stops at a cut-off age can lead to the false idea that cancer risk stops, which is not the case. Decisions about screening should take into account age, life expectancy, comorbidities and women's preferences (including risk perception). Mammography is more effective (10) compared to in younger women (as suggested by the experts surveyed in this study) because breast density decreases with age (15) and there are less benign breast diseases in the elderly population, leading us to suggest that, if continued, screening should be clinical and mammographical. Finally, the optimal interval between screenings may be at least two years, as this time interval is the most common one, and because there are fewer intervals of cancers with advancing age (16).

Onco-Geriatric Assessment in Elderly Women With Breast Cancer

The concept of frailty does not have a consensual definition because there is no patho-physiological approach to explain the complexity. Some approaches to identifying frailty exist (17) but are insufficient. In clinical practice, there are screening tools for geriatric frailty, such as the G8, which identify frail elderly cancer patients and then offer them a multidimensional geriatric assessment. This score takes into account nutrition, recent weight loss, body mass index, motor skills, age, self-perceived quality of life, neuropsychological problems and polymedication. Establishing a G8 score is easy and was validated by the ONCODAGE study (18) in a cohort including 1,674 cancer patients with a mean age of 78.2 years. Attempts to improve the G8 have been proposed, including by the team of Petit-Moneger et al. (19) in 2016, who show that the addition of the four Instrumental Activities of Daily Living items improves G8 performance and is achievable in less than 10 minutes. The use of the modified G8 demonstrated better diagnostic performance in detecting patterns suggestive of frailty, according to Martinez-Tapia et al. (20) in 2022. More specifically, using the G8 in breast cancer did not affect the survival of patients in whom a mastectomy was proposed in a study of 177 patients over 70 years of age (21): it is a screening tool and not predictive of mortality.

Screening tools are to be distinguished from the comprehensive geriatric assessment (CGA), which requires consultation with a geriatric specialist. The main domains explored by the CGA are social environment, functional, nutritional, cognitive, and psychological status (depression, anxiety), mobility, falls, fatigue, sensory disturbances, comorbidity, medications, and presence of geriatric syndromes (22). Unlike geriatric frailty screening tools, the CGA has a prognostic value, and may lead to changes in oncologic treatment (23, 24, 25), and also decrease treatment morbidity (26). Some authors suggested that patients would benefit from the addition of quality of life assessment to the CGA (27, 28).

The 2021 EUSOMA/SIOG (6) guidelines state that a screening tool should be considered in the decision making process. Likewise, we recommend that this geriatric frailty screening – with or without CGA – should be performed in frail elderly patients, because it allows a personalized approach with identification of geriatric elements that may complicate cancer management. It also allows the optimization of medical treatment of comorbidities.

Breast Cancer Treatment in Elderly Women

Therapeutic management of breast cancer becomes more delicate in the elderly population. Compared to younger patients, not only do elderly patients have more comorbidities, but also a higher risk of dying from other causes. Indeed, tailoring of breast cancer treatment should also take into account life expectancy, as it has been highlighted in this survey and in the 2021 EUSOMA/SIOG guidelines and in 2021 ACR and SBI guidelines. However, estimating life expectancy is challenging. In this context, de Glas et al. (29) published in 2016 a predictive algorithm (PREDICT) that could accurately predict the 5-year overall survival in older patients with breast cancer, although it did not include any geriatric assessment. More recently, van der Plas-Krijgsman et al. (30) published another predictive tool named PORTRET, which is able to predict recurrence, overall survival, and other-cause mortality in older patients (≥65 years) with breast cancer. These predictive tools are useful in the decision making process in order to adapt treatment to life expectancy and could be implemented in clinical routine practice.

In this survey, participants stated that axillary surgery was globally similar in elderly women. Of interest, the 2021 EUSOMA/SIOG guidelines specified that sentinel lymph node biopsy "*remained the standard of care for staging the axilla in patients with clinically and radiologically negative axilla*" (6), however these guidelines indicated that axillary surgery could be omitted in "*patients with cT1N0 luminal A-like tumours or short life expectancy*" (6). Still, axillary lymph node dissection (ALND) indications may be different according to the survey's paticipants and the guidelines in patients with a positive sentinel lymph node, and axillary radiotherapy should be preferred (6). Converesely, primary endocrine therapy could also be considered instead of surgery, especially when life expectancy is <5 years (6). Breast surgery remains not contraindicated in most cases, lumpectomy and sentinel lymph node biopsy can be easily performed with local anesthesia and sedation. Moreover, oncoplastic surgery was not contra-indicated in both the survey's responses and in the 2021 guidelines. Finally, breast reconstruction may be offered to elderly women, according to patients' comorbidities and desire, but it has higher complication rates compared to younger women (31), and some techniques, such as free flaps, are usually contraindicated.

Regarding adjuvant treatments, participants answered that they followed adjusted chemotherapy and radiotherapy protocols in elderly women. Indeed, hypofractionated radiotherapy may be an alternative in cases of restriced mobility or geographic distance. Several studies have demonstrated that hypofractionated protocols may be an acceptable alternative to normofractionated protocols in elderly breast cancer patients (32-34). Accordingly, the 2021 EUSOMA/SIOG guidelines stated that hypofractionated protocols should be preferred (6). Adjuvant chemotherapy in estrogen receptor-positive human epidermal growth factor receptor-2 (HER2)-negative breast cancer has lesser benefit compared to younger women. Indeed, a recent study of 1,969 women aged 70 years and over with a high-risk molecular signature score found that chemotherapy + endocrine therapy versus endocrine therapy alone did not result in a significant benefit in overall survival, suggesting therefore that adjuvant chemotherapy could be omitted even for high-risk patients (35). Nonetheless, for triple

negative phenotypes and HER2-positive cancers, chemotherapy and targeted therapies should be considered as there is a benfit in elderly women (36).

Of interest, the vast majority of this survey participants stated that a dedicated multidisciplinary meeting for discussion of older women with breast cancer should be considered. This point was not included in the EUSOMA/SIOG 2021 guidelines and there is no literature published on this topic, to our knowledge. One could suggest that this practice should be encouraged in specialized centers with enough activity and a dedicated team, and could improve not only breast cancer treatment, but also the global management of elderly women.

This survey provided a general picture of current international practices of breast cancer in elderly women. It underlined that breast cancer management in elderly women remains complex and sometimes heterogeneous and not consensual. Different topics were investigated, and are summarized in Table 3. Regarding the continuation of screening in elderly women, the experts surveyed in this study and the international recommendations are in favor of continuing screening on an individual basis. In addition, it is important to emphasize that existing guidelines and predictive models of life expectancy can be an assistance in the treatment decision. Furthermore, the establishment of specific multidisciplinary committees can also be an approach for difficult cases. Breast cancer in elderly women is a central issue in the future of senology, and therefore an urgent matter that needs addressing.

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Original Article

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Role of Reassurance and Proper Mechanical Support Advice on Quality of Life and Pain Relief in Patients of the Mastalgia-A Prospective Follow-up Study at A Tertiary Care Center in a Developing Country

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ABSTRACT

Objective: To study the effect of reassurance and proper mechanical support on quality of life (QOL) and visual analogue score (VAS) pain assessment in patients with mastalgia at a range of follow-ups.

Materials and Methods: A prospective follow-up study was conducted among women aged 15–45 years, complaining of breast pain without any abnormality detected clinically and radiologically. After consent to participate and enrollment, all the study participants were counseled and reassured about the non-neoplastic nature of the disease and about wearing proper mechanical support/Bra; this was repeated at each follow-up. VAS was used to assess the pain intensity perceived by the woman at each follow-up, post intervention. The Short Form-36 (SF–36) scale was used to evaluate health related QOL (HRQOL).

Results: Among 80 patients, 31.2% were wearing a Bra of fabric other than cotton, 21.2% were wearing a loose fit mechanical support/Brassiere, while 10% were not wearing any mechanical support at baseline. The overall mean VAS score was significantly reduced with each follow-up, indicating decreased perception of breast pain over time. There was a significant difference between the mean SF-36 score between base line and after three months (p<0.0001). Mean scores in all domains of the SF-36 increased. The greatest reduction in mean VAS score was seen in 26–35 years age group and women with a body mass index <18.5 kg/m^2.

Conclusion: Reassurance and wearing proper mechanical support/Bra are effective for improving QOL and alleviating breast pain/mastalgia. These simple processes should be used for the management of mastalgia.

Keywords: Mastalgia, breast pain; quality of life; reassurance; mechanical support; body mass index

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Key Points

- Mastalgia is seen to have a connection with various conditions such as anxiety, stress, body mass index, improper diet, improper education regarding proper breast support, psychological symptoms of somatization disorders, especially where mastalgia is resistant to treatment.
- Two most common issues that trouble the patient of mastalgia are firstly, fear of suffering from breast cancer and secondly, breast pain or discomfort affecting their quality of life.
- Reassurance and wearing proper mechanical support/Bra are crucial in improving the quality of life and alleviating the breast pain/mastalgia and should be utilized by breast physicians in clinical decision making for its management.

Introduction

Mastalgia or breast pain is a very common complaint among women, especially in the reproductive age group (1, 2). It is either cyclical or non-cyclical, and when cyclical may mirror the menstrual cycle of the patient. Mastalgia may adversely affect daily life by reducing the quality of life (QOL) and lead to anxiety for the patient (3-5). Usually, the two most common issues that trouble the patient with mastalgia are, firstly, fear of breast cancer and secondly, breast pain or discomfort affecting their QOL (6).

QOL of an individual is based on various factors, including physical, social, economical and/or mental factors. Perception of pain is one of the most prominent physical factors affecting the QOL of any

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individual. Pain is a constant struggle with sensory impairment and affect the emotional state of the patient, who may have different pain tolerance, and hence react differently; this may eventually impact their QOL (7).

The prevalence of breast pain in the Indian population is 47.33% (8). The etiology of mastalgia is unclear despite the advances made in medicine. Of all the disease conditions associated with mastalgia, the most common is benign breast disease. Mastalgia has also been associated with various conditions, such as anxiety, stress, body mass index (BMI), improper diet, poor education regarding proper breast support, and psychological symptoms of somatization disorders, especially when mastalgia is resistant to treatment (6, 9, 10). In such cases, reassurance and some lifestyle modifications have been found to be effective (11, 12).

Various treatment modalities have been used and proposed to treat patients suffering from mastalgia, but reassurance and proper mechanical support has been found to be most effective (10, 13, 14). Mastalgia has been reported to affect an individual's daily activities and QOL (6, 8). It is reported that when reassured about the absence of breast cancer, almost 85% women show relief of pain and psychological stress and anxiety (11).

There is little research into this topic in the Indian population. Thus, the present study was planned with the aim of investigating the effect of reassurance and advice about mechanical support in improving the QOL and alleviating the pain of mastalgia.

Objectives: To study the effect of reassurance and advice about proper mechanical support on health-related QOL (HRQOL) at baseline and three months follow-up and to investigate pain perception [visual analogue score (VAS)] in patients with mastalgia at 15 days, and one and three months follow-up.

Materials and Methods

Study Design: Prospective follow up study.

Study Setting: Outpatients Department of Surgery of a tertiary care Centre of Lucknow.

Study Period: December 2020 and June 2022 (18 months).

Study population: All female patients presenting with breast pain in the Outpatients Department of General Surgery of a tertiary care center in Lucknow, India.

Inclusion criteria: Any female patient aged 15–45 years with breast pain was included in the study.

Exclusion criteria:

1. Females with breast pain because of inflammatory causes or any fibrocystic disease.

2. Females with breast cancer.

3. Females with congenital anomalies of the breast.

4. Females who have not yet achieved menarche.

5. Patient already diagnosed to have somatoform disorder.

6. Females refusing to participate in the study.

Sample Size: Finite Population Correction has been applied to the sample size formula

$n = N*X / (X + N - 1)$, where, $X = Z_{\alpha/2}*2*p*(1-p) / d2$, $Z_{\alpha/2}$-critical value of the normal distribution at $\alpha/2$ (for a confidence level of 95%, $\alpha = 0.05$ and the critical value is 1.96), p – Estimated sample proportion i.e., Proportion of females of reproductive age group who showed reduction in pain after using a proper fitted bra/mechanical support (value is 32%) (13), d – Margin of error for appropriate level of precision (value is 0.075), N – Estimated population size i.e. approximate frequency of reproductive age females with mastalgia attending the hospital during the study period (value is 2880). At 95% confidence interval and power of 80%, the minimum sample size would be 72 patients. However, taking 10% dropouts, the final sample size required was 80 patients.

Ethical Considerations: Ethical approval for the study was obtained from the Institutional Ethical Committee of the Tertiary Care Centre (IEC no/date: 83/21 - Dr. Ram Manohar Lohia Institute of Medical Sciences).

Data Collection Procedure

Any female patient presenting with complaints of breast pain and with no abnormality detected in physical, radiological and histological examination and fulfilling the inclusion criteria was invited to participate. After giving informed written and verbal consent, the VAS was explained to them. This was followed by obtaining a detailed history which included breast pain history (duration of symptoms, cyclical, or non-cyclical) and concluded with a physical examination. Appropriate investigations (ultrasound of both breast and axilla, mammography and fine-needle aspiration cytology) was advised as per symptoms and signs. A pretested, predesigned proforma was used to record relevant information from each individual patient.

Reassurance was given by counseling that symptoms were not associated with any major or serious breast conditions, including cancer. Reassurance was reinforced by describing the normal findings from investigations. After reassurance, the female was counseled regarding wearing a proper fitted mechanical support/Bra, including advice about comfort, adequate fit, good support, and ideal fabric. Fabric preferance was cotton over other fabrics due to its non-stretchability, being good for sensitive skin, absorbance of sweat so lowering infection risk, provision of skin breathability and provides firm support. The right size was identified using the bra size chart and measuring the over and under bust size in centimeters. The right strap is the one that sits over the shoulder perfectly, doesn't dig in the skin or fall off shoulder. The right band sits perfectly around the rib cage and should form a level straight line around the torso. The cup should snug the breast covering the front and sides of the breast.

All patients were followed-up at 15 days, and one and three months post intervention. At every visit, VAS score was assessed, breast support and breast pain chart were checked, and data was recorded on a predesigned proforma and counseling was repeated.

Short-Form Health Survey (SF-36)

The HRQOL of the patients was evaluated by the SF-36 scale. The questions were converted into Hindi and then the patients were asked to mark their answers. The SF-36 scale consists of 36 items consisting of eight subscales, which includes physical role due to emotional issues and functioning, general health, bodily pain, vitality or energy, mental

and social health. Maximum score is 100, and the obtained scores vary between 0 and 100 scores for each subscale. Higher scores imply good physical and mental health where as a low score signifies deteriorated health. SF-36 is a commonly used tool to measure HRQOL (15).

Statistical Analysis

The data was analyzed using SPSS, version 24.0 (IBM Inc., Armonk, NY, USA). Descriptive summary using frequencies, percentages, graphs, mean, and standard deviation was used to present study results. Probability (*p*) was calculated to test statistical significance at the 5% level of significance. The statistical test for comparison of mean VAS score at each follow up was done using the repeated measures ANOVA test.

Results

More than half (58.8%) were wearing cotton mechanical support/Bra, while 31.2% were wearing a Bra of other fabric and 10% were not wearing any mechanical support. When bra fit was investigated, 45% females were wearing a normal fitting bra, 23.8% were wearing a tight fitting bra while 21.2% were wearing a loose fitting bra (Table 1).

The overall mean VAS score reduced with each follow up thereby decreasing the breast pain. There was a significant statistical difference among the mean VAS score between baseline and follow-up ($p<0.0001$) (Table 2).

The overall mean SF-36 was significantly higher at the third follow up when compared to the baseline indicating a perceived improvement in the HRQOL ($p<0.0001$) (Table 3). At baseline the scores indicated poor HRQOL in all the domains of the SF-36 score with very low values in domains like physical role, pain, general health and emotional role difficulty. There was a significant increase in the mean scores in all the domains of SF-36 scale (Table 4).

VAS scores varied with both age of the respondents and their BMIs. In terms of age grouping, there was a significant difference in the mean VAS score at first, second and third follow up ($p<0.05$). The mean VAS score after three months was 2.17±1.19, 2.36±0.67 and 1.80±0.64 among 15–25, 26–35 and 36–45-year-old women, respectively. Maximum reduction of VAS score occurred in the 26–35 years age group from baseline, as shown in Figure 1.

There was a significant difference in the mean VAS score at first, second and third follow-up ($p<0.05$) in terms of BMI grouping. The mean VAS score after three months was 2.00±0.0001, 2.10±0.9, 1.94±0.6 and 2.32±0.75 among females with BMI <18.5, 18.5–22.9, 23–24.9 and ≥25 kg/m^2, respectively with maximum reduction of VAS score among females with BMI <18.5 kg/m^2 from baseline, as shown in Figure 2.

Discussion and Conclusion

Mastalgia among women may be very painful and can account for 80% of breast complaints referred to the outpatient department. It is an entity largely ignored both scientifically and clinically. The two most common concerns of patients presenting with mastalgia are the fear of breast cancer and the presence of severe pain affecting their QOL (13). Mastalgia negatively affects a women's QOL (15). Most patients with mastalgia can be managed well with reassurance and after receiving advice about wearing proper mechanical support or a bra, the HRQOL improves. The present study prospectively assessed women with mastalgia and concluded that reassurance and advice on wearing a well-fitted and supporting bra played a significant role in alleviating their pain.

The study observed a significant decrease in breast pain of the study participants following repeated counselling for wearing a proper fitted bra and reassuring them regarding the natural history and possible causes of symptoms and non-neoplastic nature of the current symptoms. This was reflected in their mean VAS score which reduced significantly at each follow up indicating the alleviation in breast pain. The scientific evidence behind wearing a proper mechanical support bra is that active breast movement on its weak suspensory ligaments contributes considerably to mastalgia, so good external support by a proper fitted bra relieves most of the patient's symptoms (13).

Similar findings were reported by Hafiz et al. (12) that reassurance plus bra-fitting advice provided relief for most women. If symptoms persist, the addition of topical non-steroidal anti-inflammatory drugs (NSAIDs) provides relief in 70–92% of women. In a systematic review by Kataria et al. (16) it was reported that up to 70% of women wear improperly fitted bras. Thus, it is important to ensure that the patient is fitted with sufficiently supportive and well-fitting brassiere. It is especially useful in women endowed with large breasts.

The QOL assessed using the SF-36 was significantly higher at the third follow-up when compared to baseline, which indicates improvement in the HRQOL. At baseline the QOL was poor in all the subscales of the SF-36 score, especially emotional health, role limitations as a result of physical health, localized pain and general health. However, significant improvements were seen in all subscales over the duration of the study.

Table 1. Distribution of study participant on basis of fitting of mechanical support/bra at the first visit (n = 80)

Parameter	Class Interval	Frequency	Percentage
Fabric	Cotton	47	58.8
	Other	25	31.2
	Not wearing	8	10.0
Fitting	Tight fit	19	23.8
	Normal Fit	36	45.0
	Loose Fit	17	21.2
	Not wearing	8	10.0

Table 2. Mean VAS score of the study participants at various follow ups

Parameter	Baseline	First follow-up	Second follow-up	Third follow-up	f-value	*p*
VAS score (n = 80)	5.96 ± 0.83	5.11±1.14	3.89±0.81	2.13±0.77	832.671	**0.0001**

VAS: visual analogue score

A few similar studies have been done on patients with mastalgia and their QOL. Saeed and Ali (7) studied the impact of psychological intervention on QOL in patients of mastalgia. Prior to psychological interventions, there was no significant difference in both groups in SF-36 scale. However, after psychological intervention, the participants in Group I who received psychological interventions had significantly higher scores on all sub-scales of SF-36 (7).

Similar to our study, Kannat et al. (6) found that the QOL of patients with mastalgia was lower than that of the control group, and the sub scales of physical function (p = 0.04), body pain (p = 0.02), general health (p = 0.03), and energy (p = 0.008) were significant.

A study compared the QOL amongst eastern and western populations in Turkey. According to SF-36 results, the mean score of physical, physical role difficulty and social functions were found to be lower in the eastern group than in the western group (p = 0.029, p = 0.002, and p = 0.001, respectively). The mean scores in both groups were similar to the baseline mean SF-36 scores subscales of the present study (15). These studies did not evaluate the pre-post change in the SF-36 score after intervention.

The present study observed maximum reduction in mean VAS score at three months post intervention. Hadi (13) conducted a randomized trial in 200 women with mastalgia, where 100 women received treatment with danazol and the other 100 were asked to wear sports bras for 12 weeks. In the danazol group, 58% reported relief of symptoms (with drug side effects in 42%), while in the bra group, 85% had relief of symptoms. Sports bras have a proper mechanical support and fit which can relieve pain by reducing the overstretching of the Cooper's ligament (13).

Age and BMI of the female was also a significant predictor of improvement in the pain of mastalgia. The present study observed a significant statistical difference in the mean VAS score across various age groups and across different BMIs at each follow up. Maximum reduction in mean VAS score was seen in 26-35 years age group and those females whose BMI was less than 18.5 kg/m^2. This finding was similar with the study by Kocoglu et al. (12) who observed that age and BMI are important determinants of mastalgia. Other researchers have also concluded that age and BMI are important variables in the management of mastalgia (4, 10). However, our findings are contrary to the study by Raghunath et al. (8) who observed that women with low BMI had higher risk for mastalgia as compared to those with normal BMI (RR = 1.063) or high BMI (RR = 1.685) and hence improvement of pain also varied accordingly (7). This is attributed to the fact that BMI, mastalgia and psychological stress are very well correlated, and this parameter was not seen in our study.

Table 3. Mean SF-36 score of the study participants at various follow ups

Parameter	Baseline	Third follow-up	t-value	p
SF-36 score (n = 80)	58.64±13.45	88.27±10.21	15.694	**<0.0001**

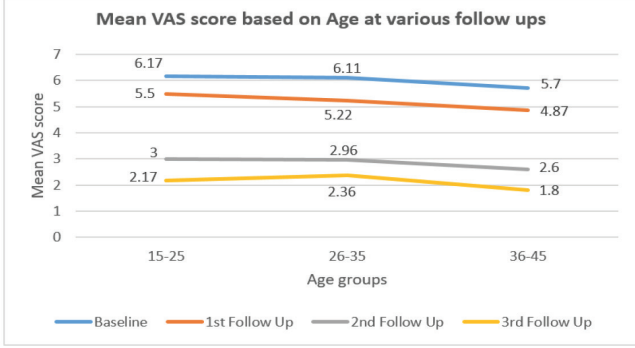

Figure 1. Mean VAS score based on Age at various follow ups

VAS: visual analogue score

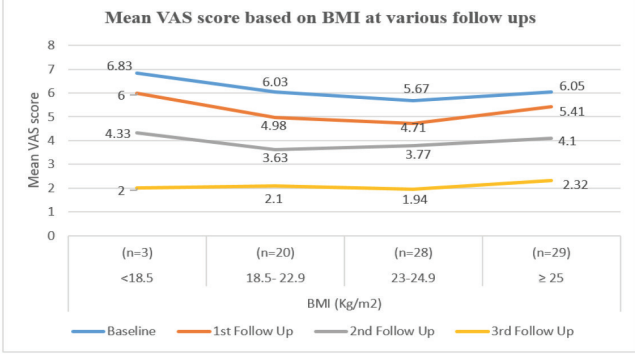

Figure 2. Mean VAS score based on BMI at various follow ups

VAS: visual analogue score; BMI: body mass index

Table 4. Mean subscales of SF-36 score of the study participants at various follow ups

Sub-scales of SF-36	Baseline	Third follow-up	t-value	p
Physical functions	72.17±12.69	92.28±5.86	12.868	<0.0001
Physical role	45.51±21.46	88.51±12.89	15.363	<0.0001
Pain	52.05±15.87	87.47±9.97	15.495	<0.0001
General health	54.07±12.36	87.55±11.58	18.098	<0.0001
Vitality (Energy)	59.74±17.21	91.75±10.38	14.246	<0.0001
Social function	66.39±13.76	93.86±12.85	13.050	<0.0001
Emotional role difficulty	49.71±19.27	81.68±14.27	11.925	<0.0001
Mental health	57.47±15.02	86.12±13.71	12.601	<0.0001

Study Limitations

The study has some limitations. Firstly, there was no control group and hence it was difficult to ascertain any association of age and BMI with the improvement of symptoms. Secondly, randomisation was not performed so there is a risk of selection bias. Still, our study gives useful insight into the importance of reassurance and wearing proper mechanical support in the alleviation of breast pain/mastalgia and its effect on HRQOL, pre- and post-counseling. Further clinical trials on a larger sample will be beneficial in generating more evidence to include this intervention in regular clinical practice of breast physicians.

Reassurance and wearing a proper mechanical support appear to be important in reducing the pain of mastalgia with maximum alleviation of pain at three months. HRQOL was significantly improved after counseling in patients with mastalgia. Age and BMI were significant factors in receiving alleviation in pain after the intervention and should be considered by breast physicians in clinical decision making.

Ethics Committee Approval: Ethical approval for the study was obtained from the Institutional Ethical Committee of the Tertiary Care Centre (IEC no/date: 83/21 - Dr. Ram Manohar Lohia Institute of Medical Sciences).

Informed Consent: Informed was written and verbal consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.P., P.R., A.S.; Concept: H.P., P.R.; Design: H.P., R.S.; Data Collection or Processing: H.P., R.; Analysis or Interpretation: H.P., S.S.; Literature Search: H.P., A.S., S.S.; Writing: H.P., P.R.

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Original Article

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Factors Related to the Knowledge and Practice of Breast Self-Examination: A Cross-Sectional Study

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ABSTRACT

Objective: Identification of the factors associated with knowledge and practice of breast self-examination (BSE).

Materials and Methods: The online survey method was used to collect data. Questions were based on an analysis of the literature and instruments used to study BSE awareness, knowledge, and practices. The study included 3536 participants, aged 18 to 71 years.

Results: Most participants (62.9%) believed they were not at risk of developing a breast cancer (BC). In the sample 459 (19%) reported they perform a BSE once a month after cessation of menstruation. The reason given for not performing the BSE by 521 (46.8%) was that they forgot, while 363 (32.6%) indicated they did not know how to perform a BSE. The mean ± standard deviation value of responses to the knowledge questions (response range 0–5) was 1.04±0.63. Almost all participants (98.6%) believed that BSE is important for the early detection of BC and that BSE awareness can be increased (96.9%).

Conclusion: Lack of comprehensive knowledge of BSE and low prevalence of regular BSE practice were observed. Education, profession, experience with BC, "not" performing BSE, and attitudes toward the importance of BSE in the early detection of BC were associated with knowledge of BSE.

Keywords: Breast self-examination; early detection of cancer; nursing; women

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Key Points

- This study offers insight into the triad of interactive factors – knowledge, attitude, and practice of breast self-examination (BSE) among Croatian women.
- BSE knowledge is related to the level of education, profession, previous experience with breast cancer, BSE practice, and attitudes toward the importance of BSE in the early detection of breast cancer.
- While the knowledge and regular practice of BSE were poor, awareness was high.

Introduction

Breast cancer (BC) is the leading cause of cancer death in women (1). At the end of 2020, there were 7.8 million women diagnosed with BC in the past five years, making it the most prevalent cancer worldwide (2).

BC incidence and mortality in Croatia are higher than in the rest of Europe (3). In Croatia, BC is the primary source of cancer and accounts for a quarter of all cancers in women (4). Although one in eleven women in Croatia is already at risk of BC, a further increase in newly diagnosed cases is expected in the future (4).

Mammography, clinical breast examination, and breast self-examination (BSE) are the commonly recommended screening methods (5). With an increasing number of studies influencing screening guidelines, the benefit of BSE has become controversial. Šašková and Pavlišta (6) reported no impact of BSE on mortality, while other studies suggest that regular BSE is associated with early detection of BC (5, 7, 8), a reduction in BC mortality (8), and improvement in survival (5).

Nearly 60% of BC deaths affect low- and middle-income countries, where access to diagnostic and curative facilities is problematic, and screening programs are underdeveloped or nonexistent (8, 9). For example, in India, the introduction of annual mammography screening currently seems unattainable (10), while in most Nigerian villages, access to health services, especially comprehensive diagnostic services, is low, if not completely impossible (11).

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Hassan et al. (7) presented BSE as a highly available screening method with low cost.

Studies on BSE practices and attitudes have shown that the rate of this screening, as well as knowledge of BSE, is low among women of different ages (12, 13). Kalliguddi et al. (14) reported that the mean ± standard deviation (SD) score for the knowledge of BSE was 18.17±2.90 when the response range was 0–30, which could be defined as moderate knowledge, while only 0.5% of the study participants had good knowledge. Accordingly, the mean score for BSE was 19.11±5.08 with a response range 0–35, which is classified as poor practice.

Nurses are crucial in educating women about BC, so their experience and knowledge of BSE are needed. Furthermore, nurses' confidence and positive attitudes about the importance of BSE for the early detection of BC can increase the effectiveness of a BSE education intervention. These factors not only affect nurses' engagement in the education of women but may also have a positive impact on teaching BSE and encouraging women to perform it (15).

According to the first part of Orem's Self-Care Deficit Theory (16), the theory of self-care, women need to focus on activities to sustain life, health, and well-being. Therefore, individual self-health empowerment, spreading breast health awareness, and regular BSE as part of self-care can be crucial for the early detection of anomalies (9, 17). Some factors may influence the knowledge and practice of BSE in women, such as age (17), family history of BC, literacy, marital status, profession, and access to BSE information (18).

The aim of this study was to provide a deeper insight into the level of knowledge, attitudes, and practice of BSE among Croatian women. The study also sought to assess the correlation between knowledge levels and a) the attitudes, b) the frequency of BSE practice, and c) the sociodemographic and other characteristics of participants (age, education level, profession, and experience with BC).

While related studies worldwide (19, 20), in Europe (21, 22), and Croatia (3) are limited to a specific university, city, or population, this study includes Croatian women of different ages, education levels, and professions regardless of residence.

Materials and Methods

Design

The cross-sectional study was conducted in Croatia, from March 12 to April 10, 2021, within a higher education institution offering a 5-year degree program for nurses.

Instrument

An anonymous questionnaire designed for this study was used. It was based on an extensive analysis of the literature and instruments for examining awareness, knowledge, and BSE practice (18, 19, 23, 24) and the authors' experience in primary health care and women's health care. Preliminary interviews with five physicians and five nurses employed in gynecological clinics contributed to the initial design of the instrument. The validity of the content of the questions was validated by an expert committee, consisting of a psychology professor, a methodologist, two professors, and one nurse with an MA with experience in women's health care. Ethical validation of included questions was confirmed by a medical ethics/clinical bioethics and deontology professor. After content validation, the clarity of the questions was rated by five randomly selected female volunteers, who did not participate in the main study. The introductory part of the questionnaire contained a description of all study details (purpose, design, instructions on study anonymity, researchers' information and contact, and guidelines for completing the questionnaire). The first part of the questionnaire addressed the general characteristics of participants: age, education, profession, experience with BC, and their perception of BC risk. The second part consisted of 11 questions (closed, single/multiple-choice, and open) related to the participants' source of information and knowledge about BSE and BSE practice. The time limit for responding to knowledge questions (closed, single/multiple-choice) was 30 seconds, and for open-ended questions, one minute. The time limit was determined, based on TIMSS 2015 Item Writing Process and Guidelines (25), according to which the allocated time to complete the multiple-choice item is one minute or less, while other questions require 1-3 minutes. The absence of a time limit in studies may affect the objectivity of participant's knowledge assessment. Therefore, this method minimized the possibility of using other sources of knowledge (books, the internet, social media, etc.). There was no time limit for responding to the other questions included. The total score for variable BSE knowledge was formed as the sum of the participant's answers to five questions measuring BSE knowledge. For each question, the participant could receive one point if she answered correctly, or zero if she answered the question incorrectly (response range 0–5).

Participants

This study included 3536 Croatian women. The inclusion criteria for the study were age (≥18 years), voluntary participation, and a completed questionnaire. The criteria also implied that the participants were active members of two online women's groups on social networks. Furthermore, the criteria for selecting these groups implied a controlled female membership and group administrators' permission to conduct this study. The groups' focus is on health promotion and the exchange of knowledge and health experiences among women. The groups included nine thousand women of different ages and professions.

Data Collection

An online survey (Google Forms) was used to collect the research data. A link to the questionnaire was sent to potential participants via the joint e-platform of the two online groups. After describing the details of the study and before activating the link, the researchers obtained permission from the administrators to access the groups and conduct the study. Online data collection was used to minimize potential risks and maintain greater confidentiality of participants.

Ethical Considerations

Participation in the study was voluntary, and participants could withdraw from the study without penalty. In the introductory part of the questionnaire, participants were informed about study details and ethical aspects. Completing and sending the questionnaire to the researchers implied the participants' voluntary consent to take part in the study and the processing of their data. The data from the questionnaire ensured complete anonymity and it cannot be used to compromise the participants' identity.

Statistical Analysis

Descriptive statistics were performed for nominal variables and data are presented as count and percentages. Numerical data are presented as arithmetic mean and standard deviation. The Shapiro-Wilk test was

used to test the normality of the distribution of numeric variables. Differences in numeric variables between two independent groups were tested with Student's t-test, and between multiple independent groups with ANOVA. Differences in variables between multiple dependent groups were tested with ANOVA for repeated measurements, using multiple comparisons of arithmetic means in the dependent groups, and post-hoc analysis was tested by the Games-Howell test. Pearson's correlation coefficient was calculated to quantify the association between two normally distributed numeric variables. The statistical significance level was 0.05. The results were analyzed using IBM SPSS, version 24.0 (IBM Inc., Armonk, NY, USA).

Results

Sociodemographic Data and BC Risk Perception

This study included 3536 participants aged 18–71 years, with a mean age of 33.4±9.86 years. Approximately half of the participants, 1790 (50.6%), attained secondary education. Over a quarter (904, 25.6%) participants were health care professionals (Table 1).

Table 1. Participants' sociodemographic data and BC risk perception

Characteristics	n (%)
Age (years)	
18–19	90 (2.5)
20–29	1362 (38.5)
30–39	1099 (31.1)
40–49	748 (21.2)
50–59	214 (6.1)
60+	23 (0.6)
Education	
Primary	44 (1.2)
Secondary	1790 (50.6)
BA	792 (22.4)
MA	845 (23.9)
PhD	65 (1.9)
Profession	
Health professionals	904 (25.6)
Non-health professionals	2632 (74.4)
Experience with BC	
Personal	55 (1.6)
Family	936 (26.5)
Friend	663 (18.7)
No experience	1882 (53.2)
BC risk perception	
At risk, diagnosed with BC	35 (1)
At risk, afraid of possible diagnosis	833 (23.5)
At risk, not afraid of possible diagnosis	445 (12.6)
Not at risk	2223 (62.9)

BC: breast cancer

More than half, 1882 (53.2%), reported having no experience with BC. Most participants, 2223 (62.9%), believed they were not at risk of developing BC (Table 1).

Sources of BSE Information

Social media, television, and/or radio were reported as the main sources of information about BSE by 2338 (66.1%) of participants. Concerningly, 41 (1.2%) participants had never heard of BSE (Figure 1).

BSE Practice

In this study, 2423 (68.5%) participants reported performing BSE. As reasons for not performing BSE, 521 (14.7%) reported forgetting, while 363 (10.3%) reported that they did not know how (Table 2).

Awareness and Knowledge of BSE

Observing any visible breast lump as an important step in BSE was acknowledged by 3161 (89.4%) participants. As a correct answer, 2911 (82.3%) respondents referred to palpating the breast by circular movements in a clockwise direction, while 111 (3.1%) stated that firm pressure should be applied. Almost all participants, 3366 (95.2%), indicated that lymph nodes should be preferably palpated in the armpit during BSE (Table 3). The mean ± SD value of responses to the knowledge questions was 1.04±0.63 with the range 0–5.

The results show no statistically significant correlation between age and knowledge of BSE (r = 0.00; p = 0.95). However, there is a significant positive correlation between the level of education and knowledge of BSE (r = 0.06, p<0.01). Perhaps unsurprisingly, health professionals had significantly better knowledge of BSE than the other participants [t (1432.844) = -6.644, p<0.01].

The results show significant differences in knowledge between participants with different experiences with BC [F (3, 3532 = 7.072; p<0.01], thus participants with no experience of BC (M = 1.00, SD = 0.626) showed a significantly poorer knowledge of BSE than participants with a family member (M = 1.08, SD = 0.625), friend (M = 1.12, SD = 0.642), or themselves (M = 1.09, SD = 0.646) having been diagnosed with BC. The participants who performed BSE had significantly better knowledge of BSE than participants who did not perform BSE [t (2411.557) = 7.319, p<0.01].

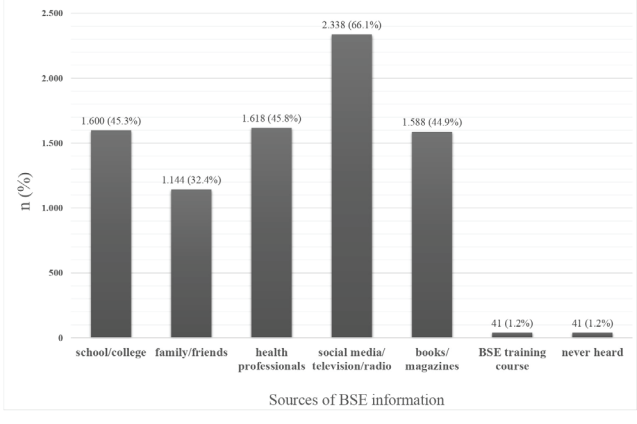

Figure 1. Sources of BSE information among participants

BSE: breast self-examination

The majority, 3488 (98.6%), consider BSE important for the early detection of BC. Participants considering this have significantly better knowledge of BSE than participants who consider the opposite [t (3534) = 2.092, p = 0.03]. As many as 2828 (80%) participants believed BSE awareness can be increased by integrating BSE content into educational curriculums, while 110 (3.1%) participants believed there was no need to increase BSE awareness (Figure 2).

Discussion and Conclusion

In this study, some participants under 20 years of age reported performing BSE, suggesting that younger participants are aware of the importance of BSE for the early detection of BC. BC in women younger than 40 years is rare, affecting between 4–6% (26), and less than 0.2% of all BCs are detected in women younger than 20 years old (27). However, young women are also more likely to have tumors with negative clinicopathologic features including higher histologic grade and more lymph node positivity (26), and consequently tend to be diagnosed at more advanced disease stages (27), contributing to a less favorable prognosis than older women (26). According to Desreux (28), most recommended screening strategies for young women are not proven efficient in terms of BC mortality, making organized population screening inefficient in women under the age of 40. BSE may be a solution to this problem.

Approximately half of the participants, 50.6%, have secondary education, which similar to an earlier survey conducted in Croatia in 2021 (29), showing that over 60% of the Croatian population, and between 55% and 65% of women, have secondary education (29).

In the present study, 62.9% of the participants believed they were not at risk of BC. Previous studies examining women's perception of BC risk and its accuracy showed that 65.7–80% of women classified in the "increased – high risk" group underestimated their BC risk (30). According to Kartal et al. (30), women who believe that family history is a minor contributor to BC risk significantly underestimate their risk. Therefore, the knowledge gap about risk factors for BC may affect risk perception.

The internet has greatly improved access to information. Social media, television and/or radio were cited as the main source of BSE information by 66.1% of the participants, which is comparable to a study from the United Arab Emirates (UAE) (57.2%) (19). In contrast, only 19.9% of women in the UAE (19) associated BSE information with a university, while 45.2% of women in this study indicated school/university as the source of BSE information. This may indicate differences in education systems. Moretti et al. (31) reported that women in Brazil perform most health searches on the internet. Hence, women have access to information about BC and screening methods and consequently

Table 2. BSE practice

Characteristics	n (%)
Performing BSE	
Yes	2423 (68.5)
No	1113 (31.5)
Frequency of BSE	
Up to five times a year	1182 (33.4)
Few days after cessation of menstruation	459 (13)
Once a week	428 (12.1)
Few days before menstruation	285 (8.1)
Any time during the month	61(1.7)
Reasons for not performing BSE	
Forgetting	521 (14.7)
Don't know how	363 (10.3)
Too young	81 (2.3)
Not interested	70 (2)
Not sure of its ability to detect a breast cancer	52 (1.5)
Fear of positive finding	26 (0.7)

BSE: breast self-examination

Table 3. Participants' knowledge of BSE

Characteristics	n (%)
Visual examination while performing BSE includes looking	
At your breasts in the mirror	1738 (49.2)
For dimpling or puckering of the skin	1937 (54.8)
At your breasts while lying on the bed	1105 (31.3)
For any visible lumps	3161 (89.4)
For nipple discharge	2761 (78.1)
For changes in nipple appearance, position, or an inverted nipple	2535 (71.7)
At breast position on the chest	784 (22.2)
Manual inspection while performing BSE includes	
A pattern: circular movements in a clockwise direction	2911 (82.3)
A pattern: dividing the breast into quadrants	704 (19.9)
Light pressure	564 (16)
Medium pressure	2328 (65.8)
Firm pressure	111 (3.1)
Using the entire length of the fingers	1107 (31.3)
Using all fingers of one hand	1442 (40.8)
While performing BSE, the right breast is palpated with	
Right hand	202 (5.7)
Left hand	2822 (79.8)
Both hands	512 (14.5)
While performing BSE, lymph nodes are palpated	
In the neck area	956 (27)
In the elbow area	46 (1.3)
In the armpit area	3366 (95.2)
In the collarbone area	1165 (32.9)
Between the breasts	554 (15.7)
BSE should be performed	
While having a bath	2157 (61)
While lying on the bed	1162 (32.9)
While standing	2561 (72.4)
In half-lying position	174 (4.9)

BSE: breast self-examination

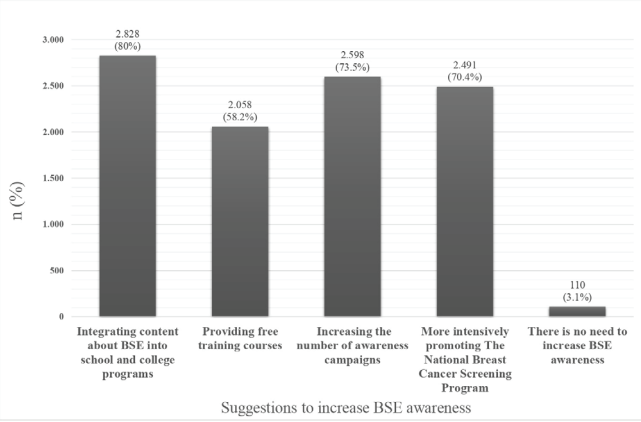

Figure 2. Suggestions to increase awareness about the importance of BSE

BSE: breast self-examination

become more aware of the importance of BSE in the early detection of BC. It appears they lack the motivation to perform it regularly.

Despite the benefits of BSE, numerous studies have shown that the screening rate is low among women of different ages. In the present study, 31.5% of participants reported that they did not perform BSE. In a study conducted among high school students in Turkey, 73% of participants did not perform BSE (12). Similar results were observed in studies among female students in Egypt (92.6%) (32), the UAE (77.3%) (33), among health care professionals in North West Ethiopia (67.5%) (20) and women of different ages in Ghana (72.5%) (13). According to Dinas et al. (22), 33–43% of women perform BSE every month. In this study, only 13% of participants perform BSE every month and at the right time (after menstruation) (34). If we disregard the right timing, 22.8% of participants in this study perform BSE monthly, more than 17.9% in Africa (8), 15.2% in Vietnam (18), and 19.6% in the UAE (19). However, more women are reported to perform regular BSE in Russia (32%), Malaysia (41%), and Poland (56.7%) (8). Although BSE is the most affordable option for the early detection of BC (8), most women in the present study did not perform BSE at the recommended frequency or at all.

As the main reason for not performing BSE, 14.7% of participants reported "forgetting", which is more than in Egypt (5.9%) (32) but less than in the UAE (28.8%) (19). Moreover, 10.3% of participants don't know how to perform BSE, which is less than 32.4% in the UAE (19) and 47.7% in Egypt (32). A study conducted in Ghana reported that 61% of participants did not know anything about BSE and were not taught how to perform it (13). On a positive note, only 2% of women in the present study reported having no interest in BSE, compared to 35% in the study conducted in Egypt (32) and 20.7% in the study conducted in the UAE (19). This question provided the option to write a response (if none of the offered suited), so some participants reported they do not practice BSE because they have annual mammograms or their gynecologist performs a clinical breast examination. Despite having reached the recommended age for mammography screening, women still self-detected abnormalities that led to a BC diagnosis (11). Moreover, most early breast tumors are self-discovered, and most early self-discoveries are because of BSE (11).

According to the mean of the responses, the participants in the present study have insufficient knowledge of BSE. Poor BSE knowledge has been observed in other studies (11, 13). However, in the present study, participants with a higher level of education also had better knowledge of BSE, which can be explained by longer-term "exposure" to specific contents during formal and/or non-formal education. In previous studies, there was also a significant correlation between the level of education and knowledge of BC (13), as well as between the level of education and knowledge on how to perform BSE (17). In a study conducted among Iranian healthcare professionals, the level of education was significantly associated with the practice of BSE (35).

Nurses play an important role in health care by defining women's BC information needs and teaching them how to perform BSE. BSE is an evidence-based practice and thus nurses should be trained in proper BSE techniques and be a primary resource for the patient to demonstrate and evaluate adherence to BSE. The health care professionals in this study had significantly more knowledge of BSE than other participants, due to their "exposure" to content about BC and BSE during education, but also because of their duty to promote health and motivate patients to participate in screening programs for the early detection of BC. Some studies suggest that health care professionals have a satisfactory knowledge of BSE (34, 36), while others indicate that their knowledge and behaviors need development (21, 24, 35). In these studies, many deficiencies concerning beginning age (24), timing (21, 24), frequency (21, 24), BSE techniques (21, 24), and practice after menopause (24) were found.

The present study found that participants with no experience of BC showed significantly poorer knowledge of BSE than participants with some experience (personal, family, friend). This could be due to getting information from a close person diagnosed with BC, their better awareness of the severity of the disease, and the importance of BSE in noticing changes at an early stage. However, regarding the correlation between the family history of BC and BSE practice, there have been studies with conflicting results. While Dagne et al. (20) revealed a correlation between the family history of BC and BSE performance, Karayurt et al. (12) showed no correlation. A study in North West Ethiopia found that women with a family history of BC were 6.5 times more likely to practice BSE than women without it (20).

The expected result was that participants practicing BSE had significantly more knowledge of BSE than participants not performing BSE. In the UAE (33) and Iran (35), the knowledge of participants who performed BSE was significantly higher than that of participants who did not perform BSE. In North West Ethiopia, women with better knowledge of BSE were 5.74 times more likely to practice BSE than those who did not know about BSE (20).

The majority of participants in the present study believed that BSE practice was important for the early detection of BC and that BSE awareness should be increased. These findings indicate high awareness and positive attitude, which are important predictors of acquiring new health education knowledge and skills. Therefore, this study related participants' attitudes toward the importance of BSE for the early detection of BC to the knowledge of BSE.

Relevance for Clinical Practice

In the future, it will be important to improve BSE knowledge and to target all age groups in BSE educational programs in Croatia. It is necessary to adopt or develop appropriate and proven educational and capacity-building measures to inform and educate women about BSE. Comparisons with similar studies indicate that the need to

raise awareness of BSE among women is almost global. Since nurses are primarily involved in cancer prevention, education, and patient care, the focus should be on their knowledge and ability to perform BSE. Therefore, providing BSE education programs will be critical to improving nurses' confidence, knowledge, implementation, and delivery of BSE. The results of this study should prompt new comparative national and global studies.

Study Limitations

Some weaknesses of this study should be noted. First, the data were collected using an online survey (non-contact). However, the time limit for responding to knowledge questions was maintained. This method mitigated the limitation of the study and allowed for a more objective assessment of the participants' knowledge. Second, the results collected on individual questions represent self-reported behaviors that risk participants having provided socially desirable responses. According to the psychological literature, this bias represents a general weakness of survey research, especially if the survey contains sensitive questions about participants' opinions, attitudes, or behaviors.

The results of this study showed a lack of comprehensive knowledge of BSE among Croatian women. Education, profession, experience with BC, not performing BSE, and attitude towards the importance of BSE in the early detection of BC were significantly correlated with knowledge of BSE. The prevalence of regular BSE practice was very low. However, most participants believed BSE was important for the early detection of BC and also believed that BSE awareness can be increased.

Ethics Committee Approval: Participation in the study was voluntary, and the participants could withdraw from the study without penalty. In the introductory part of the questionnaire, the participants were informed about the study details and ethical aspects.

Informed Consent: Completing and sending the questionnaire to the researchers implied the participants' voluntary consent to take part in the study and the processing of their data.

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Authorship Contributions

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Original Article

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Knowledge About Early Diagnosis of Breast Cancer, and Breast Cancer Risks Among Syrian Immigrants and Turkish Citizens: A Comparative, Cross-Sectional Study

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ABSTRACT

Objective: Cancer affects people regardless of being native or immigrants from developing countries. The most common form of cancer amongst displaced and immigrant women is breast cancer. This study provided a cultural comparison of early diagnosis, screening and breast cancer risks among Syrian immigrants and Turkish citizens in Turkey.

Materials and Methods: The study was performed with a descriptive, comparative and cross-sectional design with 589 women (Turkish=302, Syrian=287). A Personal Information Form and Breast Cancer Risk Assessment Form were used for data collection.

Results: The knowledge of Syrian immigrant women and behavior regarding breast self-examination, clinical breast examination, and screening with a mammogram were significantly lower than those of Turkish women (p<0.05). In addition, Syrian women's information about general breast cancer early diagnosis and screening was poorer. However, the mean breast cancer risk score was higher in Turkish women (p<0.05).

Conclusion: The data highlighted the importance of understanding locally specific barriers to breast cancer screening among immigrants and developing national programs to increase cancer education as a means of prevention.

Keywords: Breast cancer risk; early diagnosis; immigrant

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Key Points

- Early diagnosis is important in breast cancer, which is one of the most common cancers among women.
- Breast cancer early diagnosis behavior is less common among Syrian women.
- Determining the risk of breast cancer in women is important in terms of identifying priority groups for early diagnosis.

Introduction

Cancer is one of the most common and yet neglected non-communicable diseases (NCDs) among immigrants who have migrated from their own country (1). Cancer is also a growing problem among immigrants from low-income countries, and breast cancer is the most common type of cancer among immigrant women (2-4). Immigrant women experience problems accessing healthcare services as they often do not know the language of the place they have migrated to and may have little understanding of the pathways to access healthcare services (5). Patient-mediated barriers to healthcare seeking for breast cancer include many factors, such as educational level, health literacy, lifestyle behaviors and employment status, which have an effect on knowledge and awareness of breast health and symptoms and signs of breast cancer (1, 2, 6).

More than 6.2 million people took refuge in neighboring countries due to the Syrian civil war (7). In Turkey, 3,638,420 Syrian immigrants were included in the latest data (8). Turkey faces the challenge of providing healthcare to this large and vulnerable population. In a study conducted with 38,243 Syrians in Turkey between 2012 and 2015, it was reported that breast cancer was the most common form of cancer with a rate of 28.21% (9). There is little data on the breast cancer profile of immigrant populations and no epidemiological studies have been conducted with immigrants (10). In addition, breast cancer is the most common type of cancer among immigrants from the Middle East (11). Thus, it is important to determine the risk of breast cancer, which is an important problem in terms of public health, and early diagnosis behaviors. Evaluating and comparing the breast cancer knowledge level and screening behavior of Turkish citizens and

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Syrian refugees may help to understand specific barriers preventing both populations from taking appropriate action for their own health.

The aim of this study was to provide a cultural comparison of breast cancer early diagnosis, screening and breast cancer risks among Syrian immigrants and Turkish citizens living in Turkey.

Materials and Methods

Study Design

This study was a descriptive, comparative and cross-sectional study. The research was conducted between March 2019 and February 2020. The population of the study was composed of women living in ten Family Health Center regions in the city of Gaziantep. To determine the sample size, G*Power analysis was performed. The study sample was calculated as 585 women with 95% reliability and 80% power, and 589 women were contacted at the data collection stage. For Turkish citizens and Syrian immigrants, separate samples were not calculated, and the total sample was used. Gaziantep's total population is 2,154,051 and there are 461,149 Syrian immigrants. Therefore, approximately one in five people in Gaziantep is a Syrian immigrant. Syrian immigrants attend all Family Health Centers.

Inclusion Criteria

Women who were not diagnosed with breast cancer, were aged 20 and over, could speak and understand Turkish at a sufficient level to communicate with the researcher, and volunteered to participate in the study were included in the study.

Data Collection

The data were collected by the researchers through face-to-face interviews with women who applied to the Family Health Center. A Personal Information Form and Breast Cancer Risk Assessment Form were used for data collection.

Personal Information Form: This form consists of 19 questions about demographic and descriptive information about the participants (12-14).

Breast Cancer Risk Assessment Tool: The Breast Cancer Risk Assessment Tool, designed by the American Cancer Society, includes 20 items and six dimensions, which are age, familial breast cancer history, personal breast cancer history, age of giving birth, age of menstruation and body structure. A score below 200 is considered low risk, a score between 201 and 300 is considered moderate risk, a score between 301 and 400 is considered high risk, and a score over 400 is considered the highest risk. Each dimension includes different risk factors for breast cancer and the scoring is done accordingly (15, 16) (Table 1).

Ethical Consideration

Before commencement of the research, ethical approval was obtained from the Clinical Research Ethics Committee of Gaziantep University (decision no: 2019/93; date: 13.03.2019). Institutional approval was obtained from the Gaziantep Provincial Health Directorate. Informed consent of the participants was obtained during the study.

Statistical Analysis

Data were evaluated using SPSS, version 21.00 (IBM Inc., Armonk, NY, USA). The conformity of the data to normal distribution was evaluated with the Shapiro-Wilk test. In the evaluation of the data, percentage, arithmetic mean and standard deviation were used as descriptive statistics. Chi-square test was used to compare information about breast self-exam (BSE), clinical breast exam (CBE) and mammography. Independent groups t-test was used to compare mean risk scores. A p value lower than 0.05 was considered statistically significant.

Results

Of the 589 women who participated in the study, 51.3% were Turkish and 48.7% were Syrian. The great majority of the Turkish participants had received primary education and above. The large majority of the Syrian participants, however, were only literate or primary school graduates. In terms of marital status, 75.8% of the Turkish participants and 88.5% of the Syrian participants were married. A large percentage of the women were housewives, while the percentage of working women was greater among Turkish participants (32.1%). The income status of Turkish participants was found to be higher (Table 2).

Table 1. Breast cancer risk assessment tool

Risk factor	Category score
Age	
<30	10
30-40	30
41-50	75
51-60	100
≥60	125
Familial breast cancer history	
No	0
One maternal and/or paternal aunt/grandmother	50
Mother or sister	100
Mother and sister	150
Mother and two sisters	200
Personal breast cancer history	
No	0
Yes	300
Age of giving birth	
First birth before the age 30	0
First birth after the age 30	25
No child	50
Menstruation age	
≥15	15
12–14	25
≤11	50
Body structure	
Underweight	15
Normal	25
Overweight	50

When questioned about BSE, 62.3% of Turkish participants and 36.2% of Syrian participants knew how to perform a BSE and this was a significant difference (p<0.05). The percentage of Syrian women who had received BSE education was lower, that the number of those performing BSE was smaller, and that the frequency of those performing BSE correctly was significantly lower than that of Turkish women (p<0.05) (Table 2).

On investigating knowledge of CBE, 31.5% of Turkish participants and only 3.5% of Syrian participants had knowledge of the CBE, which was significantly different (p<0.05). It was found that the number of Syrian women who had had CBE done was low and that their knowledge of the frequency with which CBE should be carried out was significantly lower than Turkish women (p<0.05) (Table 3). Rates of knowledge about mammography were significantly (p<0.05) higher among Turkish participants (74.5%) compared to Syrian participants (20.9%). More than five times as many Turkish participants (16.6%) had had mammography screening compared to only 3.5% of Syrian women (p<0.05). Rates of women knowing the correct time to have mammography screening were 39.7% in Turkish participants and 11.5% in Syrian participants, and this difference was again significant (p<0.05) (Table 3).

The mean risk scores of participants based on age were 39.88±36.81 in Turkish participants and 33.78±27.42 in Syrian participants. Syrian participants' age risk scores were found to be significantly lower (p<0.05). When family history was evaluated, there was a high rate in both groups for the response "no cancer at all" and that there were no background risks. Although a high percentage of women in both groups had given birth to their first child "before the age of 30", Syrian participants (93%) had lower risk scores in terms of age at first birth. Mean birth risk scores were 13.99±22.06 in Turkish participants and 3.31±12.28 in Syrian participants (p<0.05). In terms of participants' menstruation risk scores, the total risk score was significantly lower in Turkish participants (p<0.05). Mean body type risk scores of groups were 33.28±14.65 in Turkish participants and 30.96±14.08 in Syrian participants, and this was also significantly different (Table 4).

When total risk scores were evaluated, 90.1% of Turkish participants and 91.6% of Syrian participants were included in the "low risk" group. However, the total mean risk score was lower in Syrian participants and that this lower rate was significantly different (p<0.05) (Table 4).

Discussion and Conclusion

In this study, the knowledge about, and having a history of undergoing breast examination (BSE and CBE) and mammography among 589 Turkish and Syrian immigrant women who attended Family Health Centers was evaluated in relation to breast cancer risk.

Since there is no effective prevention for breast cancer, early diagnosis of the disease is a very important step in management. BSE, CBE and mammography are screening methods that should be performed in order to make an early diagnosis of breast cancer. Within the scope of the cancer prevention and screening program published by the Ministry of Health, it is recommended that women over the age of 20 perform a BSE at least once a month (17). The behavior, knowledge and education of Turkish women participants in terms of performing BSE were significantly better than those of Syrian women. BSE is recommended

Table 2. Descriptive characteristics of the participants

		Turkish (n / %)		Syrian (n / %)	
Variable(s)		302	51.3	287	48.7
Education	Illiterate or primary school	125	41.3	223	77.7
	Middle school	31	10.3	46	16.0
	High school	64	21.2	14	4.9
	University	82	27.2	4	1.4
Marital status	Married	229	75.8	254	88.5
	Single	73	24.2	33	11.5
Employment status	Housewife	205	67.9	259	90.2
	Working	97	32.1	28	9.8
Income status	Less than expenses	105	34.8	206	71.8
	More than expenses	45	14.9	15	5.2
	Equal to expenses	152	50.3	66	23.0
BMI groups	18.8–24.5	87	28.8	91	31.7
	25–29.9	138	45.7	116	40.4
	≥30	74	24.5	80	27.9
Breast disease	Yes	5	1.7	5	1.7
	No	297	98.3	282	98.3
		Turkish	**Syrian**	**t**	**p**
Average age at first birth		21.25	18.37	**10.665**	**<0.001**
Average first menstrual age		13.28	13.22	0.748	0.455

t: independent samples t-test; BMI: body mass index

for the detection of palpable breast tumors, and it has been reported to be effective in increasing awareness of breast health in women, especially in developing and underdeveloped countries (17). In three different studies conducted in Turkey, the frequency of performing BSE once a month was reported as 8.6%, 19.7% and 29%, respectively (13-15). In contrast, Özoğul and Sucu Dağ (14) reported that 74.0% of the participants in their study performed BSE, while 55.4% of the women in a study in Malaysia had prior knowledge of BSE (15), and in a study conducted in Cameroon, three out of four of the participants had heard of BSE, but that only 60% performed BSE (16). In Nigeria, approximately half of the respondents (58.2%) had heard of BSE, whereas only 5.3% stated that they performed BSE monthly, as recommended (17). In the present study, twice as many Turkish women as Syrian women knew about and performed BSE. This difference may be because Turkish women found it easier to access breast health information and did not have language problems. A further contributing facto may have been their higher education and income levels.

The Turkish Ministry of Health also recommends that women aged over 20 have a CBE done once every two years, while women aged between 40–69 should have a CBE done annually (17). Amongst the participants in the present study participants' knowledge related to the age at which and the frequency with which women should have a CBE was inadequate, but that a significantly higher percentage of Turkish participants gave correct answers. Worringly, a high percentage of women in both groups did not have CBE done. The reported rate of CBE in Turkey varied between 7.1%, 15.5%, 39%, and 63.75% (12-14). Turkish Ministry of Health data showed that 60.9% of women in Turkey had never had CBE (18). Kwok et al. (19) reported the annual rate of CBE among Arabic women in Australia to be 21.4%. In the present study, it can be argued that the low rate of undergoing CBE was because the participants were younger and that they did not have a history of breast tumors. Furthermore, it can be suggested that Syrian women's lack of knowledge and their cultural structure had a significant effect. Although Turkish citizens and Syrian immigrants have a common background, geography and religious belief, there are major cultural differences. Immigrant communities tend to be more closed and maintain traditions aimed at preserving their culture (19). There are wide cultural differences from family relations, nutrition, clothing, and use of health services to language. While Turkish citizens will communicate more easily when accessing and using health services, Syrian immigrants are more disadvantaged in this regard. This may have caused Syrian women to be less likely to seek screening and to apply to a health institution only in case of illness.

Table 3. Comparison of information about BSE, CBE and mammography

Variable(s)		Turkish (n / %)		Syrian (n / %)		x^2	*p*
	302	51.3	287	48.7			
Knowing about BSE	Yes	188	62.3	104	36.2	39.839	<0.001
	No	114	37.7	183	63.8		
Receiving BSE training	Yes	121	40.1	56	19.5	29.575	<0.001
	No	181	59.9	231	80.5		
Case of performing BSE	Yes	127	42.1	56	19.5	34.911	<0.001
	No	175	57.9	231	80.5		
Frequency of performing BSE	Once a month	50	16.6	13	4.5	25.864	<0.001
	Sometimes	52	17.2	61	21.3		
	Every 2-3 months	108	35.8	54	18.8		
Case of having CBE done	Yes	74	24.5	32	11.1	17.780	<0.001
	No	228	75.5	255	88.9		
Reason for having CBE done	Breast complaint	29	9.6	6	2.1	4.958	0.084
	Advice of HP	18	6.0	13	4.5		
	Own opinion	27	8.9	13	4.5		
At what age is CBE done?	Knowing	95	31.5	10	3.5	78.602	<0.001
	Not knowing	207	68.5	277	96.5		
How often is CBE done?	Knowing	93	30.8	10	3.5	76.065	<0.001
	Not knowing	209	69.2	277	96.5		
Knowing about mammography	Yes	225	74.5	60	20.9	169.267	<0.001
	No	77	25.5	227	79.1		
Case of having mammography	Yes	50	16.6	10	3.5	27.484	<0.001
	No	252	83.4	277	96.5		
Time of mammography	Knowing	120	39.7	33	11.5	61.018	<0.001
	Not knowing	182	60.3	254	88.5		

X^2: chi-square; CBE: clinical breast exam; BSE: breast self-exam; HP: health professional

In Turkey, the Ministry of Health breast cancer screening program recommends women between the ages of 40–69 years to have mammography every two years (17). For women at average risk of breast cancer, the American Cancer Society recommends that those aged 40 to 44 years have the option to begin annual mammography, those aged 45 to 54 years should undergo annual mammography, and those aged 55 years or older may transition to biennial mammography or continue with annual mammograms. Women should continue screening as long as their overall health is good and they have a life expectancy of 10 years or more (20). In the present study Turkish women had significantly better knowledge of mammography, mammography screening behavior and correct knowledge of mammography screening time than Syrian women. Obaji et al. (21), in a study from Nigeria, showed that 13.4% of participants had knowledge of mammography, while in a study from Saudi Arabia, 61% of women aged between 20 – 50 years had knowledge of mammography and that 18.2% of them had had mammography (22). Studies from different regions of Turkey reported rates of mammography varying between 8.6% and 57.9% (12-14). However, Turkish Ministry of Health data reported that 71.1% of women aged 40 years and over in Turkey had never had a mammogram (18). In a study carried out with Chinese women living in the USA, 71.1% of women aged 40 and over had mammography done (23). Kwok et al. (19) determined the rate of having mammography every two years among Arabic women in Australia as 40.3%. In a study conducted with Korean women aged over 40 years living in USA, the percentage of women having mammography screening at any time in their lives was 78%, while the percentage of those having screening done in the past year was 38.6% (24). In the present study, reasons for Turkish women having better knowledge about mammography knowledge may once again be ascribed to access to information and fewer communication problems. The low mammography screening rates may be due to the younger age in the study cohort.

Interestingly, Syrian participants' age risk scores were significantly lower than those of Turkish participants. The prevalence of cancer increases with age. In Turkey, the prevalence of breast cancer is 0.1 per 100,000 in the 15–19 years age group, while this rate increases to 153.7 per 100,000 in the 65–69 age group (25). The average age of Syrian immigrants registered in our country is 22.6 years, while

Table 4. Comparison of mean risk scores

Category risk score		Turkish (n = 302) n / %		Syrian (n = 287) n / %		t	p
Age	<30	133	44.0	101	35.2	2.273	0.023
	30–40	79	26.2	122	42.5		
	41–50	45	14.9	52	18.1		
	51–60	28	9.3	6	2.1		
	≥60	17	5.6	6	2.1		
Mean ± SD age risk score		**39.88±36.81**		**33.78±27.42**			
Familial breast cancer history	No	259	85.8	236	82.2	-0.867	0.386
	One aunt/grandmother	20	6.6	35	12.2		
	Mother or sister	19	6.3	16	5.6		
	Mother and sister	4	1.3	0	0		
Mean ± SD family history risk score		**11.59±31.01**		**13.76±29.75**			
Age of giving birth (first birth)	Before the age of 30	213	70.5	267	93.0	7.208	<0.001
	After the age of 30	9	3.0	2	0.7		
	No child	80	26.5	18	6.3		
Mean ± SD birth risk score		**13.99±22.06**		**3.31±12.28**			
Menstruation age	≥15	43	14.2	28	9.8	-2.363	0.018
	12–14	246	81.5	236	82.2		
	≤11	13	4.3	23	8.0		
Mean ± SD menstruation risk score		**24.65±6.42**		**26.03±7.68**			
Body structure	Underweight	65	21.5	67	23.3	1.958	0.051
	Normal	111	36.8	124	43.2		
	Overweight	126	41.7	96	33.4		
Means ± SD body type risk scores		**33.28±14.65**		**30.96±14.08**			
Risk total score	Below 200; low risk	272	90.1	263	91.6	3.415	0.001
	201–300; medium risk	29	9.6	24	8.4		
	301–400; high risk	1	0.3	-	-		
Mean ± SD total risk score		**123.39±57.15**		**107.84±53.16**			

t: independent samples t-test; SD: standard deviation

according to the 31st December 2019 data, the average age of the population of Turkey was 32.4 years (26). Although breast cancer is the most common type of cancer among immigrants from the Middle East (11), there was no breast cancer in either participant group in this study. As the study cohort was relatively young the risk scores may have been lowered.

When family history is investigated, a high proportion of both groups reported "no cancer at all" and that background risks were absent in both groups. In a study conducted in Iran, there was a history of breast cancer in the families of 37.5% of participants (27). In a study carried out in Turkey, breast cancer history was not found in the families of 91.7% of women (28). In general, prevalence in developed regions of the world is high (over 80 per 100,000), while in developing regions it is low, though increasing (less than 30 per 100,000) (29). As Turkey belongs to the developing category, this may explain this result. Moreover, this situation may be due to the fact that the participants in our study had a lower risk of breast cancer in terms of average age.

When birth risk scores were assessed, a high percentage of women in both groups had given birth to their first child "before the age of 30". The age at first birth of 93% of Syrian participants was "before the age of 30" and they had lower risk scores. According to 2018 Turkey Demographic and Health Survey data, the median birth age of Turkish women was 23.3 years (30). In studies conducted with similar groups, it was found that rates of adolescent (aged 12–19 years) pregnancies among Syrian immigrants were significantly higher than those of women of Turkish origin (31-33). It is known that together with migration, women's social and economic status changes, and that marriages at an early age in women increase. Forced marriage at an early age is an increasing problem among Syrian girls who migrate from Syria to neighboring countries. Syrian families believe that child marriage will reduce poverty and that it will protect their daughters from the physical and sexual violence that girls frequently face. However, forced marriage at an early age increases rates of early pregnancy (34).

Evaluation of body type risk scores showed that 41.7% of Turkish women and 33.4% of Syrian women were "obese" and that mean body type risk scores were significantly higher in Turkish participants. According to the 2018 TNSA data, 59% of women living in our country were overweight or obese (30). In a study carried out with Syrian immigrants living in Turkey, it was reported that 65.2% of women had a body mass index of 25 and above (35). In a similar study, antenatal weights of Syrian immigrants and Turkish women were examined, and the rate of overweight women in both groups was high (32). It can be hypothesized that because most of the women were housewives, and the social lifestyle they have adopted, has led to their becoming increasingly overweight.

When the total breast cancer risk scores were evaluated, both groups were in the "low risk" group. An earlier Turkish study reported that 98.5% of women had a low risk of breast cancer (28). However, breast cancer remains the most frequently seen type of cancer among women in Turkey. The low risk of breast cancer in the present study was consistent with earlier findings. Breast cancer is the second most common cause of death in the world. Globally, approximately one in six deaths, while in our country, about one in five deaths, are due to cancer (25). Deaths from breast cancer can be prevented with changes in lifestyle, early recognition of risk groups, and establishment of early diagnosis behaviors.

Study Limitations

Limitations of this study include that it was performed in ten Family Health Centers of a single city. In addition, the fact that the data collected from Syrian immigrants are based only on personal recall is a further limitation. Finally, the research results cannot be generalized beyond the participant groups.

This study showed that the risk of breast cancer was low in both groups, but that Turkish women had adopted behavior more conducive to early diagnosis. Breast cancer among immigrants and displaced persons has become a growing concern among health providers, host governments, and humanitarian organizations with limited resources to promote breast cancer early diagnosis and screening, and to reduce risk factors. It is critically important to understand the current state of breast cancer knowledge, education and access to care. We hope that the study findings will contribute to potential interventions to improve the quality of care, and to increase awareness of breast cancer and achieve diagnosis at an early stage in this already disadvantaged group of women.

Ethics Committee Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Gaziantep University (decision no: 2019/93; date: 13.03.2019).

Informed Consent: Informed consent of the participants was obtained during the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.S.K.; Design: H.S.K., E.Ç.G.; Data Collection or Processing: H.S.K.; Analysis or Interpretation: E.Ç.G.; Literature Search: H.S.K., E.Ç.G.; Writing: H.S.K., E.Ç.G.

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Original Article

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Risk Factors Associated With Sentinel Lymph Node Metastasis in Clinically Node-Negative Breast Cancer

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ABSTRACT

Objective: Sentinel lymph node biopsy (SLNB) is the standard of care for axillary staging in clinically node negative breast cancer. If predictive factors for sentinel lymph node (SLN) metastasis could be identified, it would allow selection of candidates for SLNB and omit axillary surgery in those with the lowest risk of axillary lymph node involvement. The aim of this study was to determine risk factors associated with SLN metastasis in breast cancer patients in Bahrain.

Materials and Methods: Patients with clinically node-negative breast cancer who underwent SLNB at a single institution between 2016 and 2022 were identified from the pathology database. Patients who had failure of localization of SLN, those with bilateral cancers and those treated for a local recurrence were excluded.

Results: A total of 160 breast cancer patients were retrospectively analyzed. Of these, 64.4% had a negative SLNB and 21.9% of all cases underwent axillary dissection. The following parameters emerged as predictors of SLN metastasis in univariate analysis: age; tumour grade; ER status; presence of lymphovascular invasion (LVI) and tumor size. On multivariate analysis, age was not independently associated with the incidence of SLN metastasis.

Conclusion: This study showed that high tumour grades, presence of LVI and large tumour size were all risk factors related to axillary metastasis after SLNB in breast cancer. In the elderly, the incidence of SLN metastasis appeared to be relatively low, providing an opportunity to de-escalate axillary surgery in these patients. These findings may allow for the development of a nomogram to estimate the risk of SLN metastasis.

Keywords: Axillary lymph node dissection; axillary treatment; breast cancer; early breast cancer; sentinel lymph node biopsy

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Key Points

- Sentinel lymph node biopsy is the gold standard for axillary staging in clinically node-negative breast cancer patients.
- Identification of predictive factors for sentinel lymph node metastasis may allow de-escalation of axillary surgery in certain patients.
- Previous studies have shown several risk factors and predictive models for sentinel lymph node metastasis, with limited external generalisability.
- This study suggests that sentinel lymph node biopsy can be omitted in elderly patients.

Introduction

Axillary lymph node status is the most important prognostic factor in patients with early breast cancer, particularly for deciding adjuvant therapy (1). Historically, axillary lymph node dissection (ALND) was routinely performed for staging and to achieve local control, irrespective of nodal status, but this was associated with significant morbidity including lymphoedema, impaired shoulder movements and arm sensation (2). Sentinel lymph node biopsy (SLNB) has emerged as an alternative to ALND and is the standard of care for axillary staging in all clinically node negative patients (3). Compared to axillary dissection, SLNB has been shown to be a feasible and reliable method for axillary staging, while avoiding the unnecessary morbidity of an ALND (4, 5). Recently, there has been a trend towards de-escalating axillary surgery and treatment in breast cancer patients, even in the presence of axillary lymph node metastasis, with reduced patient morbidity and without compromising oncological outcomes, as supported by the ACOSOG Z0011, AMAROS and SINODAR ONE trials (6-8).

The underlying pathways of lymph node metastasis remain unclear (9). The incidence of axillary lymph node involvement in those with

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clinically negative lymph nodes undergoing SLNB is approximately 25-33%, meaning that a larger number of patients are being overtreated with increased morbidity, the need for pathologists should intraoperative frozen section be performed with associated prolonged operative time and increased healthcare costs (10-12). If predictive factors for sentinel lymph node (SLN) metastasis could be identified, it would allow the selection of candidates for SLNB and omit axillary surgery in those with the lowest risk of axillary lymph node involvement. Previous studies described several factors, such as age, multifocal disease, tumor grade, location of the tumor, tumor size, lymphovascular invasion (LVI) and receptor status as being associated with axillary lymph node metastasis (9, 11-15). Nomograms have been developed to estimate the risk of SLN metastasis in the Western population (16, 17). However, external validation of these predictive models may be limited due to differences in other breast cancer populations (12). Bahrain has the highest incidence of breast cancer among the Gulf Cooperation Council states and a significant proportion of patients have aggressive tumours compared to Western countries, including younger age, large and high grade tumors, with more than 50% of patients in Bahrain having lymph node metastasis at the time of diagnosis (18). These differences in clinicopathological characteristics of our local population could be attributed to varying genetic and environmental factors, sedentary lifestyle and ineffective screening programmes (19).

The aim of this study was to determine risk factors associated with axillary lymph node involvement in patients undergoing SLNB and to compare the results with the literature in order identify patients that could avoid axillary staging. The study findings may also be used to develop an algorithm for predicting axillary lymph node status in this population in the future.

Materials and Methods

Patients

The study method was reviewed and performed in accordance with our institution's research ethics committee. Patients with clinically node-negative breast cancer who underwent SLNB at our institution between January 2016 and August 2022 were identified from the pathology database and included in the study. Patients who had failure of localization of SLN, those with bilateral cancers and those treated for a local recurrence were excluded. In patients who underwent neoadjuvant chemotherapy, only those who were initially node-negative and remained node-negative were included. In order to determine factors associated with SLN metastasis, the following variables were evaluated: age at diagnosis; tumour location; number of foci; tumor grade; tumor size; histological tumor subtype; LVI; estrogen receptor (ER), progesterone receptor (PR) and human epithelial growth factor receptor-2 (HER-2) status; Ki-67 proliferation index; history of neoadjuvant therapy; and number of SLNs retrieved.

Surgical Technique

The method of performing SLNB in our center involves a dual technique, using both radioactive colloid and blue dye. Subareolar injection of a radioactive (Tc-99m labelled colloid) tracer is performed a few hours preoperatively on the day of surgery. After induction of general anesthesia, isosulfan blue dye is injected into the subareolar region. A hand-held gamma probe and visual inspection for blue dye is used to retrieve the SLN.

Pathological Technique

Histopathologists examined the lymph nodes by frozen section, which was prepared using haemotoxylin and eosin stain and examined microscopically. The frozen section result was communicated to the operating surgeon within 45 minutes. The remaining tissue specimen was fixed in paraffin and slides were prepared for the histopathological examination of permanent preparations postoperatively. Axillary dissection was performed only if macrometastasis was detected in more than two SLNs or there was a single positive SLN in patients who underwent neoadjuvant chemotherapy.

Statistical Analysis

Proportions of SLN metastasis were compared among different groups of patients in terms of patient and tumor characteristics. Statistical comparison was performed using the chi-square test and logistic regression analysis. *P* values less than 0.05 were considered to be significant. Statistical analyses were performed using SPSS software, version 29.0 (IBM Inc., Armonk, NY, USA).

Results

A total of 160 breast cancer patients who fulfilled the eligibility criteria were retrospectively analyzed. Patient clinical and pathological characteristics are summarized in Table 1 and Table 2, respectively. All patients were female. The median age of patients was 53 (range 23-79) years. The majority of cases were left-sided (58.1%), with breast cancer most likely to occur in the upper outer quadrant (48.8%). Most of the patients had a single focus of disease (88.1%). Mastectomy was performed in 52.5% of patients. Invasive ductal carcinoma was the most predominant histological tumor subtype (73.1%). The majority of ductal carcinoma *in situ* (DCIS) tumors were reported to be high grade (80%), while most invasive tumors were grade 2 (51.3%). The mean tumor size was 28.6 mm. For invasive cancers, approximately half of patients had T2 tumors (48.7%). LVI was present in only 20% of cases. The majority of tumors were found to be ER- and PR-receptor positive (79.3% and 73%, respectively). Furthermore, 21.3% of invasive tumors were HER2-positive and 56% of them had high Ki-67 index above 20%. Of the patients with invasive cancer, 18.7% underwent neoadjuvant therapy. The majority of patients (64.4%) had negative SLNB with no further axillary surgery. The median number of SLN retrieved at SLNB was 3 (range 1-5). Of the cohort, 21.9% of cases underwent axillary dissection. In 21 patients (60%) who underwent ALND, no further nodal metastases was identified in the axillary tissue specimen, indicating that the SLNs were the only positive lymph nodes. When univariate and multivariate logistic regression analysis was performed, five predictors of SLN positivity were identified, including age at diagnosis, tumor grade, ER status, presence of LVI and tumor size (Table 3). Although age was associated with a positive SLNB on univariate analysis, it was not an independent risk factor for SLN metastasis on multivariate analysis.

Discussion and Conclusion

The aim of this study was to determine the clinical and pathological risk factors associated with axillary lymph node status in patients undergoing SLNB for breast cancer in a population of women from Bahrain. The following parameters were identified as independent predictors of SLN metastasis on multivariate analysis: Tumor grade; ER status; presence of LVI; and tumor size.

Table 1. Clinical and demographic characteristics of the study population

Age	
Mean	54
Median	53
Range	23–79
Tumour laterality	
Right breast	67
Left breast	93
Tumour quadrant	
Central	16
LIQ[a]	8
LOQ[b]	15
UIQ[c]	34
UOQ[d]	78
Disease focality	
Unifocal	141
Multifocal or multicentric	19
Surgery	
Mastectomy	84
Breast conserving surgery	76
Neoadjuvant therapy	
Yes	28
No	122
Sentinel lymph nodes	
Mean	2.96
Median	3
Range	1–5
Axillary dissection	
Yes	35
No	125

[a]Lower inner quadrant, [b]Lower outer quadrant, [c]Upper inner quadrant, [d]Upper outer quadrant

Table 2. Histological characteristics of the study population

Tumour type	
DCIS[a]	10
IDC[b]	117
ILC[c]	16
Other	17
Tumour grade	
DCIS	
Low	0
Intermediate	2
High	8
Invasive	
Grade I	40
Grade II	77
Grade III	33
Tumour size (in mm)	
≤20	69
>20	91
T-stage	
Tis	10
T1	62
T2	73
T3	15
Lymphovascular invasion	
Present	32
Absent	128
Estrogen receptor status	
Positive	127
Negative	33
Progesterone receptor status	
Positive	116
Negative	44
HER2 status	
Positive	32
Negative	118
N/A	10
Ki-67 index	
≤20%	66
>20%	84
N/A	10
Nodal status	
N0	103
N1	43
N2	8
N3	6

[a]Ductal carcinoma *in situ*, [b]Invasive ductal carcinoma, [c]Invasive lobular carcinoma

LVI is an important factor in breast cancer metastasis, where the process of metastasis is considered to start by lymphangiogenesis, then LVI and finally lymph node metastasis (20). LVI has been described as the strongest independent predictor of nodal involvement (13). This finding was confirmed in the present study. Of our patients with LVI, 56.3% had positive lymph nodes after SLNB. LVI is associated with decreased survival on long-term follow-up, despite absence of nodal disease and it confers an even worse outcome in node-positive patients (9).

It was demonstrated that SLN metastasis was less prevalent in older women (≥60 years) compared to younger patients (<60 years) on univariate analysis. Older women with breast cancer show age-associated changes in the sensitivity to estrogen and usually present with less aggressive tumour biology (12). Our population of older breast cancer patients had smaller and lower grade tumors, which were ER-positive and HER-2 negative. This alteration in estrogen sensitivity

Table 3. Relationship between clinicopathological risk factors and sentinel lymph node metastasis

Age	**Metastasis present**	**No metastasis**	***p* (univariate analysis)**	***p* (multivariate analysis)**
<60	46 (28.7%)	72 (45%)	**0.029**	0.357
≥60	9 (5.6%)	33 (20.6%)		
Tumour side				
Left	32 (20%)	61 (38.1%)	0.564	
Right	23 (14.4%)	44 (27.5%)		
Tumour quadrant				
Upper	33 (20.6%)	79 (49.4%)	0.137	
Lower	11 (6.9%)	12 (7.5%)		
Multifocality or multicentricity				
Yes	5 (3.1%)	14 (8.8%)	0.155	
No	50 (31.3%)	91 (56.9%)		
Surgery				
Mastectomy	30 (18.8%)	54 (33.8%)	0.741	
Breast conserving surgery	25 (15.6%)	51 (31.9%)		
Tumour grade				
Low (grade 1)	15 (9.4%)	25 (15.6%)	**0.018**	**0.011**
High (grade 2-3)	40 (25%)	70 (43.7%)		
Tumour type				
Ductal	43 (26.9%)	84 (52.5%)	0.668	
Lobular	7 (4.4%)	9 (5.6%)		
ER receptor				
Positive	50 (31.3%)	77 (48.1%)	**0.013**	**0.009**
Negative	5 (3.1%)	28 (17.5%)		
PR receptor				
Positive	43 (26.9%)	73 (45.6%)	0.269	
Negative	12 (7.5%)	32 (20%)		
HER2 receptor				
Positive	13 (8.1%)	24 (15%)	0.588	
Negative	42 (26.3%)	79 (49.4%)		
Ki-67 index				
<20%	25 (15.6%)	42 (26.3%)	0.237	
≥20%	30 (18.8%)	58 (36.3%)		
LVI				
Present	18 (11.3%)	14 (8.8%)	**0.006**	**0.003**
Absent	37 (23.1%)	91 (56.9%)		
Neoadjuvant therapy				
Yes	10 (6.3%)	18 (11.3%)	0.516	
No	45 (28.1%)	87 (54.4%)		
Tumour size				
<20 mm	18 (11.2%)	45 (28.1%)	**0.045**	0.214
≥20 mm	37 (23.1%)	50 (31.2%)		
T stage				
T1-T2	48 (30%)	87 (54.3%)	**0.031**	**0.020**
T3	7 (4.37%)	8 (5%)		

and combination of these favorable histological parameters may be contributing factors for the reduced incidence of SLN metastasis in our older patients. In line with recent trends towards de-escalating axillary surgery, our results support the Society of Surgical Oncology Choosing Wisely guideline recommendation against routine SLNB in elderly patients with hormone receptor-positive and HER2-negative breast cancer, as axillary staging does not influence adjuvant therapy or outcomes in these patients (21).

Tumor size has been described as one of the strongest predictive risk factors for SLN metastasis after LVI and is also associated with higher probability of detection of metastasis after axillary dissection (15). This is because larger tumours are more likely to harbor an invasive component with associated LVI (14). Relevant studies have shown that tumor size was positively correlated with lymph node metastasis and our results are consistent with this (9, 13-15). In the present study, compared with smaller tumours (≤20 mm), the risk of SLN metastasis was approximately 1.5 fold greater for tumours larger than 20 mm (26% versus 39%, respectively). In terms of T-stage, the risk for SLN metastasis was 23.6% for T1 tumours, 42.4% for T2 tumours and 50% for T3 tumours. Nevertheless, a proportion of our patients underwent neoadjuvant therapy, which affected the true tumor size and thus it may not be representative of the actual tumor burden (14).

Although there are studies linking high grade tumors with axillary lymph node metastasis (9, 15), other studies have shown no significant association between tumor grade and nodal metastasis (11, 20). In particular, one study found that increasing tumor grade did not predict a higher risk for axillary lymph node metastasis, where grade 3 tumors did not show any increased propensity to spread to regional lymph nodes and any possible over treatment of breast cancer patients on the basis of tumour grade should be discouraged (13). Approximately two-thirds of the patients in our cohort with positive SLN metastasis had high grade tumours, compared to 27% with grade 1 tumors.

ER, PR and HER-2 receptor statuses are important for directing hormonal and targeted therapies in breast cancer management. There is some controversy about the role of molecular markers in predicting axillary lymph node metastasis; some authors reported an association (15), others showed no correlation (11, 17, 22), while one study even showed an inverse relationship (13). In the present study, 60% of patients with ER-positive tumors and 70% of cases with PR-positive tumors did not have axillary nodal metastasis after SLNB. In contrast, only about a quarter of patients with HER-2 positive tumors had nodal metastasis detected after axillary surgery. On formal statistical analysis, only ER status showed a significant association with lymph node involvement.

Study Limitations

There are a few potential limitations of this study. These include its retrospective nature, patients enrolled from a single institution and relatively small sample size. In addition, patients who underwent neoadjuvant chemotherapy were included, which might have affected the results. Therefore, the generalizability of our findings is limited. However, this study is the first from Bahrain to evaluate predictive factors for SLN metastasis. Our results will not change the indications for SLNB. Even patients with high probability of lymph node metastasis are candidates for SLNB, as the majority of these patients can still avoid axillary dissection.

This study showed that high tumor grades, presence of LVI and large tumor size were independent risk factors related to SLN metastasis in clinically node-negative Bahraini breast cancer patients. These findings also suggest that, in the elderly, the likelihood of axillary metastasis after SLNB is relatively low and axillary surgery may be omitted in these patients. Our findings may allow for the development of an algorithm to predict which patients are at high risk for axillary lymph node metastasis. There are ongoing trials evaluating whether SLNB contributes to staging or local control, and the need for surgical staging of the axilla in other patient subgroups may be eliminated by non-invasive measures or observation in the future.

Ethics Committee Approval: The study method was reviewed and performed in accordance with our institution's research ethics committee.

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: H.A.A., A.D.; Concept: H.A.A.; Design: H.A.A., A.D.; Data Collection or Processing: A.Z.S., S.J.A., K.N., S.A.A., S.A.A.; Analysis or Interpretation: H.A.A., A.Z.S., A.D.; Literature Search: H.A.A., S.J.A., K.N., S.A.A.; Writing: H.A.A., A.Z.S., S.J.A., K.N., S.A.A., S.A.A., A.D.

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Original Article

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A Multicenter Study of Genotype Variation/Demographic Patterns in 2475 Individuals Including 1444 Cases With Breast Cancer in Turkey

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ABSTRACT

Objective: Breast cancer (BC) is the most common cancer type in women and may be inherited, mostly in an autosomal dominant pattern. The clinical diagnosis of BC relies on the published diagnostic criteria, and analysis of two genes, *BRCA1* and *BRCA2*, which are strongly associated with BC, are included in these criteria. The aim of this study was to compare BC index cases with non-BC individuals in terms of genotype and diagnostic features to investigate the genotype/demographic information association.

Materials and Methods: Mutational analyses for the *BRCA1/BRCA2* genes was performed in 2475 individuals between 2013-2022 from collaborative centers across Turkey, of whom 1444 with BC were designated as index cases.

Results: Overall, mutations were identified in 17% (421/2475), while the percentage of mutation carriers in cases of BC was similar, 16.6% (239/1444). *BRCA1*/*BRCA2* gene mutations were detected in 17.8% (131/737) of familial cases and 12% (78/549) of sporadic cases. Mutations in *BRCA1* were found in 4.9%, whereas 12% were in *BRCA2* ($p<0.05$). Meta-analyses were performed to compare these results with other studies of Mediterranean-region populations.

Conclusion: Patients with *BRCA2* mutations were significantly more common than those with *BRCA1* mutations. In sporadic cases, there was a lower proportion with *BRCA1/BRCA2* variants, as expected, and these results were consistent with the data of Mediterranean-region populations. However, the present study, because of the large sample size, revealed more robust findings than previous studies. These findings may be helpful in facilitating the clinical management of BC for both familial and non-familial cases.

Keywords: Breast cancer; *BRCA1*; *BRCA2*; genomic profiling; population study

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Key Points

- Breast cancer
- *BRCA1*
- *BRCA2*
- Genomic profiling
- Population study

Introduction

Breast cancer (BC) is a condition affecting approximately two million people per year, globally. The incidence is estimated as 1:8 in women and 1:833 in men (1). The clinical diagnosis of BC relies on the published diagnostic criteria (2). Two genes have been identified as being strongly associated with BC but not all cases are due to inherited factors. These two genes are breast cancer (*BRCA*) 1 and *BRCA2*. The *BRCA1* gene, located on chromosome 17, codes for breast cancer type 1 susceptibility protein. This gene has 22 exons distributed over approximately 110 kb of genomic DNA. In contrast with the *BRCA1* gene, the *BRCA2* gene has 27 exons over approximately 84.2 kb of genomic DNA on chromosome 13 (3). To date, more than 3242 disease-causing mutations have been identified in either *BRCA1* or *BRCA2* (4). It has been suggested that patients with BC without detected variants in *BRCA1* or *BRCA2* probably have mutations on other cancer related genes or large gene deletions, somatic mosaic mutations, and mutations in un-analysed gene noncoding regions of *BRCA1* and/or *BRCA2* (1, 2).

There is clinical interest in whether the phenotypic presentation of BC differs depending on disease-causing variants in *BRCA1* or *BRCA2*. Early studies from Mediterranean countries, even the population-based studies, which have reported genotype/phenotype correlations have not found any evidence for phenotypic differences between patients with *BRCA1* mutations vs. patients with no identified mutation or between patients with *BRCA1 vs. BRCA2* mutations (4-8). These studies, however, tend to have relatively small sample sizes. The largest and most recent studies showed *BRCA2* was found more frequently in individuals with BC in the region. The main studies included patients without family history but are also limited by the low number of index cases in the study group. On the other hand, *BRCA2* positivity reported with relatively higher frequencies in the Mediterranean region of Turkey when compared with other international studies (9, 10).

In this study, mutational analysis for the *BRCA1* and *BRCA2* genes was performed in 2475 individuals, of whom 1444 had been diagnosed with BC and were considered index cases. Comparisons were then made between BC patients and those without BC and between patients with by *BRCA1* or *BRCA2* variants in terms of diagnostic and demographic features to describe the genotype/demographic association in BC in this population. Mutation type, either protein truncation or missense, was also compared in terms of phenotypic features, as well as with the probands with positive family histroy. These latter comparisons were made to determine whether there was additional prognostic information that can be provided to families, based on genetic test results or mode of inheritance.

Materials and Methods

Patient Characteristics

Patients with a diagnosis of BC and healthy individuals with family history of BC were enrolled between 2013 and 2020 with informed written consents. The study was approved by the institutional review boards of all participating universities and the ethics board at Cukurova University. All the cases were diagnosed with invasive ductal BC with no other types of cancers or any other precancerous conditions. Similarly, individuals that were studied for screening were not affected with any other malignancies. For the familial studies, individuals who had family history of invasive ductal BC were included. Patient selection was made according to the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines (11, 12). Enrolled patients were evaluated by all our collaborators from Turkey, including from the Mediterranean, Aegean, Black Sea, Central Anatolia, Marmara, Eastern Anatolia, and Southeastern Anatolia Regions, and also from Northern Cyprus. As this study was conducted retrospectively, patient selection criteria were re-evaluated according to the up-to-date ASCO and NCCN guidelines prior to genetic analyses. The goal was to identify if variants were present in the *BRCA1* and *BRCA2* genes in these patients with invasive ductal BC. For familial BC cases that were enrolled, we included only the index patients for phenotypic analyses.

Subjects were enrolled in our research protocol through six different centers across Turkey and Cyprus. Clinical information was not available for every feature of BC on every participant. Some patients were referred and enrolled in the mutation screening process without sending sufficient clinical information to determine diagnostic status. Some of other demographic data, such as ethnicity, were not included due to the heterogeneity of the Turkish population, and lack of the consent of the majority of patient cohort further information. Patients who had no information, such as family history, were not included in the demographic analysis. We have, however, included them in the description of the mutations. Patients who were under 18 years of age, who were all index cases, were included. Moreover, patients who were under 30 years of age and carried *TP53* mutations were excluded, due to the purpose of our study.

Screening and Classification of Genetic Variations

DNA was extracted from peripheral blood lymphocytes of both healthy individuals and BC cases. Next generation sequencing was performed for all coding exons and exon-intron junctions of the *BRCA1* and *BRCA2* genes. In addition, Multiplex Ligation-dependent Probe Amplification (MLPA) was performed for 591 AGENTEM's primary index patients, as this is the national reference center for *BRCA1*/*BRCA2*. MLPA assay was not performed in the other collaborative centers. Nucleotide change was considered as pathogenic, a polymorphism or a variant of unknown significance (or unclassifiable variant) when it was novel and parents were unavailable for study. American College of Medical Genetics and Genomics (ACMG) criteria were followed for variant classification. The variations that were not identified in the Human Gene Mutation Database (HGMD) and The Single Nucleotide Polymorphism Database (dbSNP) or any other clinical databases (ClinVar and VarSome) were assessed as novel changes. Novel variants were then investigated through *in silico* analysis for variant classification. *In silico* analysis tools, including PolyPhen, Mutation Taster, CADD, SIFT, BLOSUM, PhyloP, GeneSplicer, B-SIFT, MaxEntScan, QCI Inferred Activation, BayesDel, DANN, SpliceAI, GenoCanyon, fitCons, MUT Assesor, Varity, FATHMM-XF, FATHMM-MKL, EIGEN PC, LRT were used, based on the genomic location, population frequencies, type and possible impacts on protein of the variations.

Statistical Analysis

The BC disease features for the following groups were compared using student's t test: (1) gene loci mutated *BRCA1* versus *BRCA2* and (2) familial versus sporadic using Graph Pad Prism (8.0.1.) Patient clinical findings were analyzed after grouping by gender, familial or sporadic, and location of mutation in *BRCA1* or *BRCA2*. As patients came from different sources and may not have all demographic criteria assessed, the numbers for each analysis varied. Only information from patients with a definite diagnosis was used for statistical analyses.

Population Comparison

GnomAD v2.1.1 data set (GRCh37/hg19) was used for the population comparison, which spans 125,748 exome sequences and 15,708 whole-genome sequences from unrelated individuals. The highest frequency of specific genetic alteration in gnomAD data set from various populations was used in order to compare our results with global data.

GnomAD v2.1.1 data set is the largest publicly available population data to date, and categorizes the populations as follows; African/African-American, Amish, Latino/Admixed American, Ashkenazi Jewish, East Asian, South Asian, Middle Eastern, European (Finnish), European (non-Finnish) and other. However, the proportion of the gnomAD population did not cluster with any of the Mediterranean populations. Therefore, it is more likely that Mediterranean populations were classified as "other", which includes individuals of mixed background, as in Turkey.

The MAF cut-off of 0.001 that is recommended for variant discovery in dominant inherited Mendelian diseases was used to classify variants as rare frequency (MAF ≤0.001) supporting variants' pathogenic effect, and common frequency (MAF ≥0.001) which are unlikely to be causative.

Results

Patient Characteristics

BRCA1 and *BRCA2* mutational analyses were performed in 2475 subjects. However, we were unable to curate all data for phenotypic features and not all subjects were interviewed for family history. Therefore we include 1444 (58.3%) cases contributing to results. Among 1444 BC patients, 737 (51%) of them had positive family history while 549 (49%) cases had no invasive ductal BC in their family. In the remaining patients (n = 158), family history of BC was unknown. Among *BRCA1*/*BRCA2* positive patients with a definite diagnosis, identification of a genetic alteration for familial patients was higher (54.8%; 131/239) than for patients with sporadic BC (32.6%; 78/239), and this was significant. The remaining variant positive patients (n = 30) were the individuals with unknown familial history of BC.

The median (range) age for all index patients (n = 1444) was 51.5 (15-88) years, and the average age was 48.6 years. Figure 1 details the demographic characteristics of our study population.

Mutation Analysis

Pathogenic mutations were identified in 218 individuals and variants of unknown significance for 139; in affected BC cases 114 of them had pathogenic variants and 85 cases had VUSs. Total variants, their pathogenicity, and internal frequencies are given in supplementary data (Supplementary Table 1). No genetic change could be identified for 2054 patients (82.9%) in total, and for 1205 (83.5%) of the BC cases. Among 737 BC cases with positive family history, 36 cases (4.9%) had variations in *BRCA1* and 95 cases (12.89 %) had variations in *BRCA2*, while 6 (4.6%) patients had genetic alterations in both genes resulting in a *BRCA1*:*BRCA2* ratio of 1/2.6. Twenty-seven of 549 patients

Table 1. Overall distribution of variant classification in *BRCA1* and *BRCA2* genes for both healthy individuals with BC diagnosed cases (n = 2475) and affected BC cases (n = 1444)

		Pathogenic	Likely Pathogenic	VUS
Both healthy individuals and BC diagnosed cases	***BRCA1***	70.1% (103/147)	11.5% (17/147)	18.4% (27/147)
	BRCA2	41.6% (118/283)	17.6% (50/283)	40.6% (115/283)
	Total	221 (51.3%)	67 (15.5%)	142 (33%)
Affected BC cases	***BRCA1***	71.4% (50/71)	11.3% (8/71)	18.3% (13/71)
	BRCA2	37.9% (66/174)	19.5% (34/174)	42.5% (74/174)
	Total	116	42	87

VUS: variant of uncertain significance; BC: breast cancer

(4.9%) without family history had variants in *BRCA1* and 51 patients (9.2%) had variants in *BRCA2*, resulting in a *BRCA1*:*BRCA2* ratio of approximately 1/2.

The mutations identified in *BRCA1* and *BRCA2* genes in all 2475 individuals were distributed as follows: 51.3% pathogenic, 15.5% likely pathogenic and 33% VUS (Table 1). Variant classifications for affected BC cases are also shown separately in Table 1.

The most frequent variants that were detected in both *BRCA1* and *BRCA2* are listed in Table 2. The most frequent variants were distributed equally across both genes. From the perspective of pathogenicity, pathogenic variants were present relatively more frequently, with nine variants. Novel genetic variations in both *BRCA*s are listed in Table 3. In contrast with the frequent variant list, *BRCA2* was more commonly found to be the site of novel variants with 14 versus one novel variant in *BRCA1*.

Clinical Features and Demographic Comparisons

The distribution of family history and the gender of cases for BC patients in this study are listed in Table 4. Phenotypes of these patients were compared by gender and mutation. Observed frequencies of clinical features listed in Table 5 for BC patients in this study. A proportion of cases were male, 20 of 1444 (1.39%) and pathogenic

Table 2. The most frequent detected variants in *BRCA1* and *BRCA2* genes

Gene	Variant	Impact	Class.[1]	Freq.[2] (%)
BRCA2	c.7689delC p.H2563Qfs*85	Frameshift	P[3]	3.92 (n = 17)
BRCA1	c.1444_1447delATTA p.I482*	Frameshift	P	3.46 (n = 15)
BRCA1	c.2800C>T p.Q934*	Nonsense	P	3 (n = 13)
BRCA1	c.4327C>T p.R1443*	Nonsense	P	3 (n = 13)
BRCA1	c.5266dupC p.Q1756Pfs*74	Frameshift	P	3 (n = 13)
BRCA2	c.1909+22delT	Inframe del	VUS[4]	2.07 (n = 9)
BRCA2	c.3836A>G p.N1279S	Missense	LP[5]	2.07 (n = 9)
BRCA2	c.9097dupA p.T3033fs*11	Frameshift	P	2.07 (n = 9)
BRCA2	c.3318C>G p.S1106R	Missense	LP	1.61 (n = 7)
BRCA2	c.3751dupA p.T1251fs*14	Frameshift	P	1.38 (n = 6)
BRCA2	c.4169delT p.L1390fs*20	Frameshift	P	1.38 (n = 6)
BRCA2	c.67+1G>A	Intronic	P	1.38 (n = 6)
BRCA2	c.8881G>A p.G2961S	Missense	VUS	1.38 (n = 6)

[1]Class.: classification; [2]Freq.: frequency; [3]P: pathogenic; [5]LP: likely pathogenic; [4]VUS: variant of uncertain significance

Table 3. Detected novel variants in *BRCA1* and *BRCA2* genes

Gene	Variant	Impact	Class.[1]
BRCA1	c.5152+23C>T	Intronic	VUS[3]
BRCA2	c.1519delA p.R507fs*2	Frameshift	LP[2]
BRCA2	c.1854C>A p.A618A	Synonymous	VUS
BRCA2	c.5647A>T p.K1883*	Nonsense	LP
BRCA2	c.5697T>A p.D1899E	Missense	VUS
BRCA2	c.6609T>A p.V2203V	Synonymous	VUS
BRCA2	c.6934G>C p.D2312H	Missense	LP
BRCA2	c.7645T>G p.C2549G	Missense	LP
BRCA2	c.7700A>G p.Y2567C	Missense	VUS
BRCA2	c.8020_8021dupAA p.I2675fs*2	Frameshift	LP
BRCA2	c.8021A>G p.K2674R	Missense	LP
BRCA2	c.8487+39T>C	Intronic	VUS
BRCA2	c.9370_9381delAACCTCCAGTGG p.N3124_W3127del	Inframe del	LP
BRCA2	c.9370_9383delAACCTCCAGTGGCGinsCT p.R3128delinsL	Missense	LP
BRCA2	c.9772G>A p.E3258K	Missense	VUS

[1]Class.: classification; [2]LP: likely pathogenic; [3]VUS: variant of uncertain significance

variations in *BRCA2* were present in two of the male BC patients. In this multicenter study, other demographic data, such as ethnicity, were not included due to the heterogeneity of the Turkish population and other legal issues in terms of the law on protection of personal data.

Subjects With A Positive Family History Versus Sporadic BC Cases

The phenotypic effects of mutation between the *BRCA1* gene and the *BRCA2* gene and BC features were investigated in 737 familial index patients and 549 sporadic BC patients. The median age was 52 years for familial index patients and 48.5 years for sporadic BC patients with average ages of 43.3 and 43.5 years, respectively. Comparison of the disease features of these two groups did not show any significant difference. However, patients with a positive family history were more likely to harbor *BRCA1/2* gene mutations than sporadic BC patients.

Impact of Mutation Types

The type of mutations in many genetic related disorders affects disease severity. To evaluate the effect of the type of mutations on the presence of BC features, we compared features of patients.

The proportions of mutations types detected are listed in Table 6.

Allele Frequency Comparison

Among a total of 220 different types of detected variations, 190 (86.4%) of them had higher allele frequencies than their aggregated gnomAD allele frequency. With a 0.001 MAF cut-off, 134 (60.9%) of the 220 variants were evaluated as rare and as all of them showed higher frequency in our study, they were considered as more likely to be pathogenic. In addition, 73.7% (56/76) of the globally common variants (MAF ≥0.001) were more frequent in our study while 20 (26.3%) showed lower frequencies than aggregated gnomAD. Distribution of common (MAF ≥0.001) and rare *BRCA1/2* variants (MAF ≤0.001) by gnomAD population and the aggregated gnomAD are given as supplementary data (Supplementary Table 2).

The frequencies of pathogenic variants and VUSs were compared across several ethnic groups and the local whole exome sequencing databases. The analysis showed that out of 28 pathogenic variants located in *BRCA1*, 31 occurred as a higher frequency than aggregated gnomAD data and distinctive populational gnomAD data. Details are given in supplementary data (Supplementary Table 2).

Table 4. Gender and family history distribution of cases

	Family history (+)	Family history (-)	Unknown family history
Female	729	537	158
Male	8	12	0
Total	737	549	158

Table 5. Phenotypic comparison of variant between genders in cases.

	Pathogenic	Likely Pathogenic	VUS
Female	113	43	87
Male	2	0	0
Total	115	43	87

VUS: variant of uncertain significance

Discussion and Conclusion

Mutations were sought in all coding exons and exon-intron junctions of the *BRCA1* and *BRCA2* genes in DNA from 2475 diagnosed and screening patients from Turkey and 221 (51.3%) previously reported pathogenic mutations, 142 (33%) VUS and 15 (3.7%) novel mutations were found, while the overall *BRCA1* and *BRCA2* mutation detection rate was 9.9%.

No mutation in *BRCA1/2* could be identified in 82.9% of all patients. Despite being one of the largest cohorts of *BRCA1/2* screening in the literature, as a limitation of our study, we were not able to examine gross deletion and duplication status of *BRCA1* and *BRCA2* genes in all mutation negative patients due to different infrastructures of collaborative centers. As noted in previous studies, the mutation detection rate varies from 2.7% to 19% for patients with positive family history but without clinical information in different populations (8, 9, 13).

One of the main focuses of this study was to pool a nationwide Mediterranean country dataset that will increase the power of further analysis for clinical interpretations, both in familial and non-familial cases and the cases with *BRCA1* and *BRCA2* mutations.

In multifactorial disorders such as cancers, correlation between genotype variation and demographic information is not as well understood as it is in Mendelian disorders. Analysis and interpretation of genetic test results should be considered with the patient's clinical and family history. This study also showed that a significant percentage of *BRCA1* and *BRCA2* variations are still classified as VUS. Thus, improvement of genetic variation databases is crucial for correct diagnosis. In the light of the fact that the genotype and phenotype correlation for BC is still controversial, these results can enhance our knowledge on this complicated, common and severe condition.

It was also observed that the most common mutations in the *BRCA1* and *BRCA2* genes in a representative Turkish population were not among the 10 most common mutations that were reported in a study that included all continents. *BRCA1* c.1444_1447delATTA p.I482* and *BRCA2* c.7689delC p.H2563Qfs*85 mutations can be considered

Table 6. Overall distribution of genetic variation types

	Frameshift	Missense	Nonsense	Intronic	In-frame dup	In-frame del
BRCA1	34	43	40	11	0	1
BRCA2	76	128	24	27	2	6
Total	110	171	64	38	2	7

to be founder mutations for Turkish population and a screening program can be planned for early diagnosis of BC (14).

We also demonstrated the importance of looking at the frequency of each variant per specific ethnic groups as opposed to the overall gnomAD frequency. Our analysis highlighted 56 pathogenic variants that had MAF ≤0.001 (Minor Allele Frequency) in the aggregated gnomAD population but were common in our population. Furthermore, when a more stringent MAF cut-off value (≤0.0001) was used, 123 pathogenic variants should be re-classified as more frequent and might be suggested as founder mutations for our population. In brief, these data also suggest that a number of variants still classified as pathogenic are not truly disease causing or the variants with the higher observed frequency are not truly benign.

The overall *BRCA1/2* mutation detection rate for patients with BC in Turkey was 9.9% in this study. The proportion of *BRCA1* to *BRCA2* mutations was approximately 2 to 2.5 for BC cases. Moreover, in patients with no family history of BC, *BRCA1* mutations accounted for 34.6% and *BRCA2* mutations accounted for 65.4% among mutation positive cases. Our study summarizes the interpretation process using the most important criteria as per ACMG guidelines, gene specific databases for analysis of the variant frequencies in the largest available population, together with local datasets and results of the computational predictions for a broadly representative but heterogeneous Turkish population.

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Ethics Committee Approval: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of from Cukurova University Ethical Committee (102-2 and 07/08/2020).

Informed Consent: All participants were informed, and signed written consent

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.O.S., N.D., S.Y.O., M.C.E., K.D., C.K.P., O.Y., L.A., O.B., S.C., E.C., A.D., T.E., S.G., K.S., S.T., B.D., F.O., D.T., M.C., O.D., P.O., S.T.B., S.G.T.; Concept: A.B.; Design: K.D., M.D., A.B., S.G.T.; Data Collection or Processing: I.B., C.M., C.R., O.S., A.A., L.A., B.D., C.O.E., N.G., M.D.,; Analysis or Interpretation: I.B., C.M., C.R., O.S., A.A., B.D., C.O.E.; Literature Search: I.B., C.M., C.R., O.S., E.A., N.B., N.G., B.D.; Writing: M.C.E., M.D., A.B., S.G.T.

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Supplementary Table 1. The detected total variants list

Gene	Variant	Variant Type	Class.	Variant Freq. (%)	n
BRCA1	c.1444_1447delATTA p.I482*	Frameshift	P	3.46	15
BRCA1	c.2800C>T p.Q934*	Nonsense	P	3.00	13
BRCA1	c.4327C>T p.R1443*	Nonsense	P	3.00	13
BRCA1	c.5266dupC p.Q1756Pfs*74	Frameshift	P	3.00	13
BRCA1	c.181T>G p.C61G	Missense	P	1.15	5
BRCA1	c.5123C>A p.A1708E	Missense	P	1.15	5
BRCA1	c.135-2A>T	Intronic	LP	0.69	3
BRCA1	c.1881_1884del p.S628Efs*3	Frameshift	P	0.69	3
BRCA1	c.3211G>T p.E1071*	Nonsense	LP	0.69	3
BRCA1	c.3333del p.E1112Nfs*5	Frameshift	P	0.69	3
BRCA1	c.3607C>T p.R1203*	Nonsense	P	0.69	3
BRCA1	c.4391_4393delinsTT p.P1464Lfs*2	Frameshift	P	0.69	3
BRCA1	c.4956G>A p.M1652I	Missense	P	0.69	3
BRCA1	c.1895G>A p.S632N	Missense	LP	0.46	2
BRCA1	c.2019delA p.E673Dfs*28	Frameshift	P	0.46	2
BRCA1	c.2077G>A p.D693N	Missense	VUS	0.46	2
BRCA1	c.2599C>G p.Q867E	Missense	LP	0.46	2
BRCA1	c.3328_3330delAAG p.K1110del	Inframe del	VUS	0.46	2
BRCA1	c.4070_4071delAA p.E1357Gfs*10	Frameshift	LP	0.46	2
BRCA1	c.4936del p.V1646Sfs*12	Frameshift	P	0.46	2
BRCA1	c.5057dupA p.H1686Qfs*9	Frameshift	LP	0.46	2
BRCA1	c.509G>A p.R170Q	Missense	LP	0.46	2
BRCA1	c.5152+23C>T	Intronic	VUS	0.46	2
BRCA1	c.535T>C p.Y179H	Missense	VUS	0.46	2
BRCA1	c.53T>A p.M18K	Missense	VUS	0.46	2
BRCA1	c.788dupG p.S264*	Nonsense	P	0.46	2
BRCA1	c.979A>G p.T327A	Missense	VUS	0.46	2
BRCA1	c.1166_1169dup p.D390Efs*2	Frameshift	LP	0.23	1
BRCA1	c.134A>C p.K45T	Missense	VUS	0.23	1
BRCA1	c.1621C>T p.Q541*	Nonsense	P	0.23	1
BRCA1	c.1637_1685delinsGAAAG p.M546Ifs*5	Frameshift	LP	0.23	1
BRCA1	c.1644T>C p.I548I	Synonymous	VUS	0.23	1
BRCA1	c.1714G>T p.E572*	Nonsense	P	0.23	1
BRCA1	c.1772T>C p.I591T	Missense	VUS	0.23	1
BRCA1	c.1888G>T p.R629I	Missense	VUS	0.23	1
BRCA1	c.1938_1947delCAGTGAAGAG p.S646fs*2	Frameshift	P	0.23	1
BRCA1	c.2611_2612delCC p.P871Vfs*31	Frameshift	P	0.23	1
BRCA1	c.2666C>T p.S889F	Missense	VUS	0.23	1
BRCA1	c.2952del p.I986Sfs*14	Frameshift	P	0.23	1
BRCA1	c.3247A>G p.M1083V	Missense	LP	0.23	1
BRCA1	c.3700_3704del p.N1234Qfs*8	Frameshift	P	0.23	1
BRCA1	c.3756_3759delGTCT p.S1253fs*10	Frameshift	P	0.23	1
BRCA1	c.3770_3771delAG p.E1257Gfs*9	Frameshift	P	0.23	1
BRCA1	c.4033C>T p.L1335L	Nonsense	VUS	0.23	1

BRCA1	c.4035delA p.E1346fs*20	Frameshift	P	0.23	1
BRCA1	c.4063_4065delAAT p.N1355del	Inframe del	LP	0.23	1
BRCA1	c.4065_4068delTCAA p.N1355Kfs*10	Frameshift	P	0.23	1
BRCA1	c.4185+21_4185+22dupTG	Inframe dup	LP	0.23	1
BRCA1	c.4366A>G p.T1456A	Missense	VUS	0.23	1
BRCA1	c.4391_4393delCTAinsTT p.P1464Lfs*2	Frameshift	P	0.23	1
BRCA1	c.4443G>T p.E1478D	Missense	VUS	0.23	1
BRCA1	c.4487C>A p.S1496*	Nonsense	P	0.23	1
BRCA1	c.493_494delCT p.L165fs*16	Frameshift	P	0.23	1
BRCA1	c.4986+6 T>C	Intronic	LP	0.23	1
BRCA1	c.4986+6T>G	Intronic	VUS	0.23	1
BRCA1	c.4987A>T p.M1663L	Missense	LP	0.23	1
BRCA1	c.5102_5103delTG p.L1722Qfs*14	Frameshift	P	0.23	1
BRCA1	c.5194-2A>G	Intronic	P	0.23	1
BRCA1	c.692C>G p.T231R	Missense	VUS	0.23	1
BRCA1	c.734A>T p.D245V	Missense	VUS	0.23	1
BRCA1	c.81-4C>T	Intronic	VUS	0.23	1
BRCA2	c.7689delC p.H2563Qfs*85	Frameshift	P	3.92	17
BRCA2	c.1909+22delT	Inframe del	VUS	2.07	9
BRCA2	c.3836A>G p.N1279S	Missense	LP	2.07	9
BRCA2	c.9097dupA p.T3033fs*11	Frameshift	P	2.07	9
BRCA2	c.3318C>G p.S1106R	Missense	LP	1.61	7
BRCA2	c.3751dupA p.T1251fs*14	Frameshift	P	1.38	6
BRCA2	c.4169delT p.L1390fs*20	Frameshift	P	1.38	6
BRCA2	c.67+1G>A	Intronic	P	1.38	6
BRCA2	c.8881G>A p.G2961S	Missense	VUS	1.38	6
BRCA2	c.1519delA p.R507fs*2	Frameshift	LP	1.15	5
BRCA2	c.7472A>T p.Q2491L	Missense	VUS	1.15	5
BRCA2	c.9317G>A p.W3106*	Nonsense	P	1.15	5
BRCA2	c.1411G>A p.E471K	Missense	VUS	0.92	4
BRCA2	c.4471_4474del p.L1491Kfs*12	Frameshift	P	0.92	4
BRCA2	c.5969delA p.D1990Vfs*14	Frameshift	P	0.92	4
BRCA2	c.8478C>A p.Y2826*	Nonsense	P	0.92	4
BRCA2	c.10095delCinsGAATTATATCT p.S3366Nfs*4	Frameshift	LP	0.69	3
BRCA2	c.1343G>A p.R448H	Missense	VUS	0.69	3
BRCA2	c.1414C>T p.Q472*	Nonsense	P	0.69	3
BRCA2	c.2808_2811delACAA p.A938fs*21	Frameshift	P	0.69	3
BRCA2	c.4081C>G p.Q1361E	Missense	VUS	0.69	3
BRCA2	c.4258G>T p.D1420Y	Missense	VUS	0.69	3
BRCA2	c.4751del p.E1584Gfs*33	Frameshift	LP	0.69	3
BRCA2	c.6550C>G p.Q2184E	Missense	VUS	0.69	3
BRCA2	c.6814delA p.R2272Efs*8	Frameshift	P	0.69	3
BRCA2	c.7007G>A p.R2336H	Missense	P	0.69	3
BRCA2	c.9052_9057delAGTAAA p.K3019_3020del	Inframe del	LP	0.69	3
BRCA2	c.9934A>G p.I3312V	Missense	VUS	0.69	3
BRCA2	c.1773_1776delTTAT p.I591Mfs*22	Frameshift	P	0.46	2
BRCA2	c.122C>T p.P41L	Missense	VUS	0.46	2

BRCA2	c.1310_1313delAAGA p.K437Ifs*22	Frameshift	P	0.46	2
BRCA2	c.1951G>T p.D651Y	Missense	VUS	0.46	2
BRCA2	c.2765dupT p.K923Qfs*13	Frameshift	P	0.46	2
BRCA2	c.3503T>C p.M1168T	Missense	P	0.46	2
BRCA2	c.4146_4148delAGA p.E1382del	Inframe del	LP	0.46	2
BRCA2	c.4243G>C p.E1415Q	Missense	VUS	0.46	2
BRCA2	c.4446_4451dupAACAGA p.E1482_T1483dup	Inframe dup	VUS	0.46	2
BRCA2	c.5312G>A p.G1771D	Missense	VUS	0.46	2
BRCA2	c.5351dupA p.N1784Tfs*3	Frameshift	P	0.46	2
BRCA2	c.5590G>A p.D1864N	Missense	VUS	0.46	2
BRCA2	c.5647A>T p.K1883*	Nonsense	LP	0.46	2
BRCA2	c.6008T>C p.I2003T	Missense	VUS	0.46	2
BRCA2	c.6080G>A p.R2027K	Missense	VUS	0.46	2
BRCA2	c.6935A>T p.D2312V	Missense	VUS	0.46	2
BRCA2	c.7544C>T p.T2515I	Missense	VUS	0.46	2
BRCA2	c.7976G>A p.R2659K	Missense	P	0.46	2
BRCA2	c.8092G>A p.A2698T	Missense	VUS	0.46	2
BRCA2	c.8452G>A p.V2818I	Missense	VUS	0.46	2
BRCA2	c.8649A>G p.P2883P	Synonymous	VUS	0.46	2
BRCA2	c.9501+4A>G	Intronic	VUS	0.46	2
BRCA2	c.9839C>A p.P3280H	Missense	P	0.46	2
BRCA2	c.9976A>T p.K3326*	Nonsense	LP	0.46	2
BRCA2	c.10037_10046delTGATAAATACinsATT p.L3346fs*35	Frameshift	LP	0.23	1
BRCA2	c.10078A>G p.K3360E	Missense	VUS	0.23	1
BRCA2	c.10089A>G p.I3363M	Missense	VUS	0.23	1
BRCA2	c.1055dupA p.Y352*	Nonsense	P	0.23	1
BRCA2	c.1114A>C p.N372H	Missense	P	0.23	1
BRCA2	c.1181A>C p.E394A	Missense	LP	0.23	1
BRCA2	c.1235C>G p.P412R	Missense	VUS	0.23	1
BRCA2	c.1570A>G p.M524V	Missense	VUS	0.23	1
BRCA2	c.1587_1590delTAAA p.F529fs*28	Frameshift	P	0.23	1
BRCA2	c.1605C>T p.A535A	Synonymous	P	0.23	1
BRCA2	c.1627C>A p.H543N	Missense	LP	0.23	1
BRCA2	c.1648G>A p.E550K	Missense	VUS	0.23	1
BRCA2	c.1773_1776delTTAT p.I591fs*22	Frameshift	P	0.23	1
BRCA2	c.1854C>A p.A618A	Synonymous	VUS	0.23	1
BRCA2	c.2264C>G p.S755C	Missense	VUS	0.23	1
BRCA2	c.2372C>A p.S791*	Nonsense	P	0.23	1
BRCA2	c.2706T>C p.A902A	Synonymous	VUS	0.23	1
BRCA2	c.2779A>G p.M927V	Missense	VUS	0.23	1
BRCA2	c.280C>T p.P94S	Missense	VUS	0.23	1
BRCA2	c.2892A>T p.K964N	Missense	LP	0.23	1
BRCA2	c.3073A>G p.K1025E	Missense	LP	0.23	1
BRCA2	c.3171_3172del p.K1058Tfs*8	Frameshift	P	0.23	1
BRCA2	c.3263dupC p.Q1089Sfs*10	Frameshift	P	0.23	1
BRCA2	c.6290C>T p.T2097M	Missense	LP	0.23	1
BRCA2	c.3302A>G p.H1101R	Missense	VUS	0.23	1

BRCA2	c.3465_3466delTT p.S1156*	Nonsense	VUS	0.23	1
BRCA2	c.349_350delCT p.L117fs*6	Frameshift	P	0.23	1
BRCA2	c.3545_3546delTT p.F1182*	Nonsense	P	0.23	1
BRCA2	c.375T>A p.D125E	Missense	VUS	0.23	1
BRCA2	c.4237A>G p.K1413E	Missense	VUS	0.23	1
BRCA2	c.426-1G>C	Intronic	P	0.23	1
BRCA2	c.4519delC p.Q1507Rfs*36	Frameshift	P	0.23	1
BRCA2	c.4531G>A p.E1511K	Missense	VUS	0.23	1
BRCA2	c.4631dupA p.N1544Kfs*4	Frameshift	P	0.23	1
BRCA2	c.4901T>C p.F1634S	Missense	VUS	0.23	1
BRCA2	c.5020delA p.S1674Vfs*8	Frameshift	P	0.23	1
BRCA2	c.5130_5133TGTA p.Y1710*	Nonsense	P	0.23	1
BRCA2	c.5153-26A>G	Intronic	VUS	0.23	1
BRCA2	c.518delG p.G173fs*12	Frameshift	P	0.23	1
BRCA2	c.5483A>G p.K1828R	Missense	VUS	0.23	1
BRCA2	c.5697T>A p.D1899E	Missense	VUS	0.23	1
BRCA2	c.5722_5723delCT p.L1908Rfs*2	Frameshift	P	0.23	1
BRCA2	c.575T>C p.M192T	Missense	VUS	0.23	1
BRCA2	c.5870T>C p.I1957T	Missense	VUS	0.23	1
BRCA2	c.5975C>T p.S1992L	Missense	VUS	0.23	1
BRCA2	c.6085_6089delGAAAA p.E2029Yfs*18	Frameshift	P	0.23	1
BRCA2	c.6231G>C p.K2077N	Missense	LP	0.23	1
BRCA2	c.6320delC p.P2107Lfs*12	Frameshift	P	0.23	1
BRCA2	c.6365T>C p.M2122T	Missense	VUS	0.23	1
BRCA2	c.6405_6409delCTTAA p.N2135fs*3	Frameshift	P	0.23	1
BRCA2	c.6468_6469delTC p.Q2157Ifs*18	Frameshift	P	0.23	1
BRCA2	c.6469C>T p.Q2157*	Nonsense	P	0.23	1
BRCA2	c.6609T>A p.V2203V	Synonymous	VUS	0.23	1
BRCA2	c.6613G>A p.V2205M	Missense	VUS	0.23	1
BRCA2	c.6614T>G p.V2205G	Missense	LP	0.23	1
BRCA2	c.6742C>A p.H2248N	Missense	VUS	0.23	1
BRCA2	c.6842G>A p.G2281E	Missense	LP	0.23	1
BRCA2	c.6934G>C p.D2312H	Missense	LP	0.23	1
BRCA2	c.7072T>C p.S2358P	Missense	VUS	0.23	1
BRCA2	c.7227T>C p.P2409P	Synonymous	VUS	0.23	1
BRCA2	c.7435+10G>A	Intronic	VUS	0.23	1
BRCA2	c.7436-1G>C	Intronic	P	0.23	1
BRCA2	c.7522G>A p.G2508S	Missense	VUS	0.23	1
BRCA2	c.7633G>A p.V2545I	Missense	P	0.23	1
BRCA2	c.7645T>G p.C2549G	Missense	LP	0.23	1
BRCA2	c.7700A>G p.Y2567C	Missense	VUS	0.23	1
BRCA2	c.771_775del p.N257Kfs*17	Frameshift	P	0.23	1
BRCA2	c.7766C>T p.P2589L	Missense	LP	0.23	1
BRCA2	c.7783G>T p.A2595S	Missense	VUS	0.23	1
BRCA2	c.7855T>C p.W2619R	Missense	VUS	0.23	1
BRCA2	c.8020_8021dupAA p.I2675fs*2	Frameshift	LP	0.23	1
BRCA2	c.8021A>G p.K2674R	Missense	LP	0.23	1

BRCA2	c.8117A>G p.N2706S	Missense	VUS	0.23	1
BRCA2	c.8155A>G p.I2719V	Missense	VUS	0.23	1
BRCA2	c.8322-47G>T	Intronic	VUS	0.23	1
BRCA2	c.8324T>G p.M2775R	Missense	VUS	0.23	1
BRCA2	c.8359C>T p.R2787C	Missense	VUS	0.23	1
BRCA2	c.8395delA p.R2799Dfs*22	Frameshift	P	0.23	1
BRCA2	c.8487+39T>C	Intronic	VUS	0.23	1
BRCA2	c.8878C>T p.Q2960*	Nonsense	P	0.23	1
BRCA2	c.8930delA p.Y2977Ffs*11	Frameshift	VUS	0.23	1
BRCA2	c.8940delA p.E2981Kfs*7	Frameshift	P	0.23	1
BRCA2	c.8953+80G>A	Intronic	VUS	0.23	1
BRCA2	c.9038C>T p.T3013I	Missense	VUS	0.23	1
BRCA2	c.9253del p.T3085Qfs*19	Frameshift	P	0.23	1
BRCA2	c.9370_9381delAACCTCCAGTGG p.N3124_W3127del	Inframe del	LP	0.23	1
BRCA2	c.9370_9383delAACCTCCAGTGGCGinsCT p.R3128delinsL	Missense	LP	0.23	1
BRCA2	c.9382C>T p.R3128*	Nonsense	P	0.23	1
BRCA2	c.9397_9398delTC p.S3133fs*16	Frameshift	LP	0.23	1
BRCA2	c.9502-12T>G	Intronic	VUS	0.23	1
BRCA2	c.9556G>C p.A3186P	Missense	VUS	0.23	1
BRCA2	c.9586A>G p.K3196E	Missense	P	0.23	1
BRCA2	c.9613_9614delGCinsCT p.A3205L	Missense	LP	0.23	1
BRCA2	c.9682delA p.S3228Vfs*21	Frameshift	P	0.23	1
BRCA2	c.9717G>A p.W3106*	Nonsense	P	0.23	1
BRCA2	c.9730G>T p.V3244F	Missense	VUS	0.23	1
BRCA2	c.9772G>A p.E3258K	Missense	VUS	0.23	1

Supplementary Table 2. Distribution of common (MAF ≥0.001) and rare variants (MAF ≤0.001) in *BRCAs* by aggregated and population specific gnomAD data

No.	Gene	Variant	Mutation Type	ACMG Class.	n	Variant Frequency (n)	Observered Allel Frequency	gnomAD Aggregated Global Frequency	gnomAD Populational Freqency	Database/ Population	
1	*BRCA1*	c.1166_1169dup p.D390Efs*2	Frameshift	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
2	*BRCA1*	c.134A>C p.K45T	Missense	VUS	1	0.23	0.020202%	0.079800%	0.001766%	gnomAD	European (non-Finnish)
3	*BRCA1*	c.135-2A>T	Intronic	LP	3	0.69	0.060606%	0.000000%	0.000000%	gnomAD	
4	*BRCA2*	c.7689delC p.H2563Qfs*85	Frameshift	P	17	3.92	0.343434%	0.000000%	0.000000%	gnomAD	
5	*BRCA1*	c.1621C>T p.Q541*	Nonsense	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
6	*BRCA1*	c.1637_1685delinsGA AAG p.M546Ifs*5	Frameshift	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
7	*BRCA1*	c.1644T>C p.I548I	Synonymous	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
8	*BRCA1*	c.1714G>T p.E572*	Nonsense	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
9	*BRCA1*	c.1772T>C p.I591T	Missense	VUS	1	0.23	0.020202%	0.000797%	0.001762%	gnomAD	European
10	*BRCA1*	c.181T>G p.C61G	Missense	P	5	1.15	0.101010%	0.319000%	0.006168%	gnomAD	European (non-Finnish)
11	*BRCA1*	c.1881_1884del p.S628Efs*3	Frameshift	P	3	0.69	0.060606%	0.000398%	0.002893%	gnomAD	Latino/ Admixed American
12	*BRCA1*	c.1886G>T p.R629I	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
13	*BRCA1*	c.1895G>A p.S632N	Missense	LP	2	0.46	0.040404%	0.000398%	0.016360%	gnomAD	Other
14	*BRCA1*	c.1938_1947delCAG TGAAGAG p.S646fs*2	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
15	*BRCA1*	c.2019delA p.E673Dfs*28	Frameshift	P	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
16	*BRCA1*	c.2077G>A p.D693N	Missense	VUS	2	0.46	0.040404%	5.840000%	9.370000%	gnomAD	Ashkenazi Jewish
17	*BRCA1*	c.2599C>G p.Q867E	Missense	LP	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
18	*BRCA1*	c.2611_2612delCC p.P871Vfs*31	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
19	*BRCA1*	c.2666C>T p.S889F	Missense	VUS	1	0.23	0.020202%	0.001195%	0.002644%	gnomAD	European (non-Finnish)
20	*BRCA1*	c.1444_1447delATTA p.I482*	Frameshift	P	15	3.46	0.303030%	0.000000%	0.000000%	gnomAD	
21	*BRCA1*	c.2952del p.I986Sfs*14	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
22	*BRCA1*	c.3211G>T p.E1071*	Nonsense	LP	3	0.69	0.060606%	0.000000%	0.000000%	gnomAD	
23	*BRCA1*	c.3247A>G p.M1083V	Missense	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
24	*BRCA1*	c.3328_3330delAAG p.K1110del	Inframe del	VUS	2	0.46	0.040404%	0.039560%	0.323600%	gnomAD	South Asian
25	*BRCA1*	c.3333del p.E1112Nfs*5	Frameshift	P	3	0.69	0.060606%	0.000000%	0.000000%	gnomAD	
26	*BRCA1*	c.3607C>T p.R1203*	Nonsense	P	3	0.69	0.060606%	0.001195%	0.005456%	gnomAD	East Asian
27	*BRCA1*	c.3700_3704del p.N1234Qfs*8	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
28	*BRCA1*	c.3756_3759delGTCT p.S1253fs*10	Frameshift	P	1	0.23	0.020202%	0.002388%	0.016320%	gnomAD	Other
29	*BRCA1*	c.3770_3771delAG p.E1257Gfs*9	Frameshift	P	1	0.23	0.020202%	0.000796%	0.003266%	gnomAD	South Asian

30	*BRCA1*	c.4033C>T p.L1335L	Nonsense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
31	*BRCA1*	c.4035delA p.E1346fs*20	Frameshift	P	1	0.23	0.020202%	0.004248%	0.009301%	gnomAD	European (non-Finnish)
32	*BRCA1*	c.4063_4065delAAT p.N1355del	Inframe del	LP	1	0.23	0.020202%	0.000399%	0.000881%	gnomAD	European (non-Finnish)
33	*BRCA1*	c.4065_4068delTCAA p.N1355Kfs*10	Frameshift	P	1	0.23	0.020202%	0.001190%	0.003280%	gnomAD	South Asian
34	*BRCA1*	c.4070_4071delAA p.E1357Gfs*10	Frameshift	LP	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
35	*BRCA1*	c.4185+21_4185+22dupTG	Inframe dup	LP	1	0.23	0.020202%	0.006964%	0.018960%	gnomAD	South Asian
36	*BRCA1*	c.2800C>T p.Q934*	Nonsense	P	13	3.00	0.262626%	0.000000%	0.000000%	gnomAD	
37	*BRCA1*	c.4366A>G p.T1456A	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
38	*BRCA1*	c.4391_4393delCTAinsTT p.P1464Lfs*2	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
39	*BRCA1*	c.4391_4393delinsTT p.P1464Lfs*2	Frameshift	P	3	0.69	0.060606%	0.000000%	0.000000%	gnomAD	
40	*BRCA1*	c.4443G>T p.E1478D	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
41	*BRCA1*	c.4487C>A p.S1496*	Nonsense	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
42	*BRCA1*	c.493_494delCT p.L165fs*16	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
43	*BRCA1*	c.4936del p.V1646Sfs*12	Frameshift	P	2	0.46	0.040404%	0.000796%	0.009925%	gnomAD	Ashkenazi Jewish
44	*BRCA1*	c.4956G>A p.M1652I	Missense	P	3	0.69	0.060606%	1.818000%	3.799000%	gnomAD	South Asian
45	*BRCA1*	c.4986+6T>C	Intronic	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
46	*BRCA1*	c.4986+6T>G	Intronic	VUS	1	0.23	0.020202%	0.000400%	0.000892%	gnomAD	European (non-Finnish)
47	*BRCA1*	c.4987A>T p.M1663L	Missense	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
48	*BRCA1*	c.5057dupA p.H1686Qfs*9	Frameshift	LP	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
49	*BRCA1*	c.509G>A p.R170Q	Missense	LP	2	0.46	0.040404%	0.003579%	0.007033%	gnomAD	European
50	*BRCA1*	c.5102_5103delTG p.L1722Qfs*14	Frameshift	P	1	0.23	0.020202%	0.000398%	0.005438%	gnomAD	East Asian
51	*BRCA1*	c.5123C>A p.A1708E	Missense	P	5	1.15	0.101010%	0.001990%	0.005784%	gnomAD	Latino/ Admixed American
52	*BRCA1*	c.5152+23C>T	Intronic	VUS	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
53	*BRCA1*	c.5194-2A>G	Intronic	P	1	0.23	0.020202%	0.000398%	0.000879%	gnomAD	European (non-Finnish)
54	*BRCA1*	c.4327C>T p.R1443*	Nonsense	P	13	3.00	0.262626%	0.002476%	0.008468%	gnomAD	Latino/ Admixed American
55	*BRCA1*	c.535T>C p.Y179H	Missense	VUS	2	0.46	0.040404%	0.000795%	0.001758%	gnomAD	European (non-Finnish)
56	*BRCA1*	c.53T>A p.M18K	Missense	VUS	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
57	*BRCA1*	c.692C>G p.T231R	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
58	*BRCA1*	c.734A>T p.D245V	Missense	VUS	1	0.23	0.020202%	0.001200%	0.002652%	gnomAD	European (non-Finnish)
59	*BRCA1*	c.788dupG p.S264*	Nonsense	P	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
60	*BRCA1*	c.81-4C>T	Intronic	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
61	*BRCA1*	c.979A>G p.T327A	Missense	VUS	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
62	*BRCA2*	c.1773_1776delTTAT p.I591Mfs*22	Frameshift	P	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	

63	*BRCA2*	c.10037_10046delTGATAAATACinsATT p.L3346fs*35	Frameshift	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
64	*BRCA2*	c.10078A>G p.K3360E	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
65	*BRCA2*	c.10089A>G p.I3363M	Missense	VUS	1	0.23	0.020202%	0.008139%	0.065350%	gnomAD	South Asian
66	*BRCA2*	c.10095delCinsGAATTATATCT p.S3366Nfs*4	Frameshift	LP	3	0.69	0.060606%	0.000000%	0.000000%	gnomAD	
67	*BRCA2*	c.1055dupA p.Y352*	Nonsense	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
68	*BRCA2*	c.1114A>C p.N372H	Missense	P	1	0.23	0.020202%	27.330000%	35.660000%	gnomAD	Ashkenazi Jewish
69	*BRCA2*	c.1181A>C p.E394A	Missense	LP	1	0.23	0.020202%	0.002398%	0.005293%	gnomAD	European (non-Finnish)
70	*BRCA2*	c.122C>T p.P41L	Missense	VUS	2	0.46	0.040404%	0.000398%	0.000879%	gnomAD	European (non-Finnish)
71	*BRCA2*	c.1235C>G p.P412R	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
72	*BRCA2*	c.1310_1313delAAGA p.K437Ifs*22	Frameshift	P	2	0.46	0.040404%	0.000411%	0.006433%	gnomAD	African/ African-American
73	*BRCA2*	c.1343G>A p.R448H	Missense	VUS	3	0.69	0.060606%	0.000403%	0.002942%	gnomAD	Latino/ Admixed American
74	*BRCA2*	c.1411G>A p.E471K	Missense	VUS	4	0.92	0.080808%	0.000000%	0.000000%	gnomAD	
75	*BRCA2*	c.1414C>T p.Q472*	Nonsense	P	3	0.69	0.060606%	0.000000%	0.000000%	gnomAD	
76	*BRCA2*	c.1519delA p.R507fs*2	Frameshift	LP	5	1.15	0.101010%	0.000000%	0.000000%	gnomAD	
77	*BRCA2*	c.1570A>G p.M524V	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
78	*BRCA2*	c.1587_1590delTAAA p.F529fs*28	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
79	*BRCA2*	c.1605C>T p.A535A	Synonymous	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
80	*BRCA2*	c.1627C>A p.H543N	Missense	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
81	*BRCA2*	c.1648G>A p.E550K	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
82	*BRCA2*	c.1773_1776delTTAT p.I591fs*22	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
83	*BRCA2*	c.1854C>A p.A618A	Synonymous	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
84	*BRCA2*	c.5266dupC p.Q1756Pfs*74	Frameshift	P	13	3.00	0.262626%	0.000000%	0.000000%	gnomAD	
85	*BRCA2*	c.1951G>T p.D651Y	Missense	VUS	2	0.46	0.040404%	0.000416%	0.000906%	gnomAD	European (non-Finnish)
86	*BRCA2*	c.2264C>G p.S755C	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
87	*BRCA2*	c.2372C>A p.S791*	Nonsense	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
88	*BRCA2*	c.2706T>C p.A902A	Synonymous	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
89	*BRCA2*	c.2765dupT p.K923Qfs*13	Frameshift	P	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
90	*BRCA2*	c.2779A>G p.M927V	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
91	*BRCA2*	c.2808_2811delACAA p.A938fs*21	Frameshift	P	3	0.69	0.060606%	0.000797%	0.001764%	gnomAD	European (non-Finnish)
92	*BRCA2*	c.280C>T p.P94S	Missense	VUS	1	0.23	0.020202%	0.004779%	0.016350%	gnomAD	Other
93	*BRCA2*	c.2892A>T p.K964N	Missense	LP	1	0.23	0.020202%	0.004428%	0.036790%	gnomAD	South Asian
94	*BRCA2*	c.3073A>G p.K1025E	Missense	LP	1	0.23	0.020202%	0.004799%	0.009723%	gnomAD	European (non-Finnish)
95	*BRCA2*	c.3171_3172del p.K1058Tfs*8	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
96	*BRCA2*	c.3263dupC p.Q1089Sfs*10	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
97	*BRCA2*	c.6290C>T p.T2097M	Missense	LP	1	0.23	0.020202%	0.008314%	0.026390%	gnomAD	Latino/ Admixed American

98	*BRCA2*	c.3302A>G p.H1101R	Missense	VUS	1	0.23	0.020202%	0.000043%	0.000934%	gnomAD	European
99	*BRCA2*	c.1909+22delT	Inframe del	VUS	9	2.07	0.181818%	11.300000%	13.800000%	gnomAD	Ashkenazi Jewish
100	*BRCA2*	c.3465_3466delTT p.S1156*	Nonsense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
101	*BRCA2*	c.349_350delCT p.L117fs*6	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
102	*BRCA2*	c.3503T>C p.M1168T	Missense	P	2	0.46	0.040404%	0.000399%	0.002892%	gnomAD	Latino/ Admixed American
103	*BRCA2*	c.3545_3546delTT p.F1182*	Nonsense	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
104	*BRCA2*	c.3836A>G p.N1279S	Missense	LP	9	2.07	0.181818%	0.000000%	0.000000%	gnomAD	
105	*BRCA2*	c.375T>A p.D125E	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
106	*BRCA2*	c.9097dupA p.T3033fs*11	Frameshift	P	9	2.07	0.181818%	0.003185%	0.006483%	gnomAD	European (non-Finnish)
107	*BRCA2*	c.4081C>G p.Q1361E	Missense	VUS	3	0.69	0.060606%	0.000000%	0.000000%	gnomAD	
108	*BRCA2*	c.4146_4148delAGA p.E1382del	Inframe del	LP	2	0.46	0.040404%	0.007223%	0.024010%	gnomAD	European (Finnish)
109	*BRCA2*	c.3318C>G p.S1106R	Missense	LP	7	1.61	0.141414%	0.000420%	0.000914%	gnomAD	European (non-Finnish)
110	*BRCA2*	c.4237A>G p.K1413E	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
111	*BRCA2*	c.4243G>C p.E1415Q	Missense	VUS	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
112	*BRCA2*	c.4258G>T p.D1420Y	Missense	VUS	3	0.69	0.060606%	0.666000%	1.880000%	gnomAD	European (Finnish)
113	*BRCA2*	c.426-1G>C	Intronic	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
114	*BRCA2*	c.4446_4451dupAACAGA p.E1482_T1483dup	Inframe dup	VUS	2	0.46	0.040404%	0.000400%	0.000885%	gnomAD	European (non-Finnish)
115	*BRCA2*	c.4471_4474del p.L1491Kfs*12	Frameshift	P	4	0.92	0.080808%	0.000399%	0.006187%	gnomAD	African/ African-American
116	*BRCA2*	c.4519delC p.Q1507Rfs*36	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
117	*BRCA2*	c.4531G>A p.E1511K	Missense	VUS	1	0.23	0.020202%	0.002840%	0.019620%	gnomAD	South Asian
118	*BRCA2*	c.4631dupA p.N1544Kfs*4	Frameshift	P	1	0.23	0.020202%	0.000710%	0.001554%	gnomAD	European (non-Finnish)
119	*BRCA2*	c.4751del p.E1584Gfs*33	Frameshift	LP	3	0.69	0.060606%	0.000000%	0.000000%	gnomAD	
120	*BRCA2*	c.4901T>C p.F1634S	Missense	VUS	1	0.23	0.020202%	0.001427%	0.003120%	gnomAD	European (non-Finnish)
121	*BRCA2*	c.5020delA p.S1674Vfs*8	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
122	*BRCA2*	c.5130_5133TGTA p.Y1710*	Nonsense	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
123	*BRCA1*	c.5153-26A>G	Intronic	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
124	*BRCA2*	c.518delG p.G173fs*12	Frameshift	P	1	0.23	0.020202%	0.003185%	0.011470%	gnomAD	African/ African-American
125	*BRCA2*	c.5312G>A p.G1771D	Missense	VUS	2	0.46	0.040404%	0.031580%	0.096690%	gnomAD	Ashkenazi Jewish
126	*BRCA2*	c.5351dupA p.N1784Tfs*3	Frameshift	P	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
127	*BRCA2*	c.5483A>G p.K1828R	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
128	*BRCA2*	c.5590G>A p.D1864N	Missense	VUS	2	0.46	0.040404%	0.001220%	0.016760%	gnomAD	Other
129	*BRCA2*	c.5647A>T p.K1883*	Nonsense	LP	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
130	*BRCA2*	c.5697T>A p.D1899E	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
131	*BRCA2*	c.5722_5723delCT p.L1908Rfs*2	Frameshift	P	1	0.23	0.020202%	0.000399%	0.003268%	gnomAD	South Asian

132	*BRCA2*	c.575T>C p.M192T	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
133	*BRCA2*	c.5870T>C p.I1957T	Missense	VUS	1	0.23	0.020202%	0.002391%	0.006535%	gnomAD	South Asian
134	*BRCA2*	c.5969delA p.D1990Vfs*14	Frameshift	P	4	0.92	0.080808%	0.000000%	0.000000%	gnomAD	
135	*BRCA2*	c.5975C>T p.S1992L	Missense	VUS	1	0.23	0.020202%	0.000709%	0.001553%	gnomAD	European (non-Finnish)
136	*BRCA2*	c.6008T>C p.I2003T	Missense	VUS	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
137	*BRCA2*	c.6080G>A p.R2027K	Missense	VUS	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
138	*BRCA2*	c.6085_6089delGAAAA p.E2029Yfs*18	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
139	*BRCA2*	c.6231G>C p.K2077N	Missense	LP	1	0.23	0.020202%	0.011660%	0.096250%	gnomAD	South Asian
140	*BRCA2*	c.6320delC p.P2107Lfs*12	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
141	*BRCA2*	c.6365T>C p.M2122T	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
142	*BRCA2*	c.6405_6409delCTTAA p.N2135fs*3	Frameshift	P	1	0.23	0.020202%	0.000416%	0.017240%	gnomAD	Other
143	*BRCA2*	c.6468_6469delTC p.Q2157Ifs*18	Frameshift	P	1	0.23	0.020202%	0.000436%	0.003910%	gnomAD	Other-South Asian
144	*BRCA2*	c.6469C>T p.Q2157*	Nonsense	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
145	*BRCA2*	c.6550C>G p.Q2184E	Missense	VUS	3	0.69	0.060606%	0.001220%	0.010160%	gnomAD	Ashkenazi Jewish
146	*BRCA2*	c.6609T>A p.V2203V	Synonymous	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
147	*BRCA2*	c.6613G>A p.V2205M	Missense	VUS	1	0.23	0.020202%	0.002446%	0.005358%	gnomAD	European (non-Finnish)
148	*BRCA2*	c.6614T>G p.V2205G	Missense	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
149	*BRCA2*	c.3751dupA p.T1251fs*14	Frameshift	P	6	1.38	0.121212%	0.000407%	0.016740%	gnomAD	Other
150	*BRCA2*	c.6742C>A p.H2248N	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
151	*BRCA2*	c.6814delA p.R2272Efs*8	Frameshift	P	3	0.69	0.060606%	0.000000%	0.000000%	gnomAD	
152	*BRCA2*	c.6842G>A p.G2281E	Missense	LP	1	0.23	0.020202%	0.000408%	0.003397%	gnomAD	South Asian
153	*BRCA2*	c.6934G>C p.D2312H	Missense	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
154	*BRCA2*	c.6935A>T p.D2312V	Missense	VUS	2	0.46	0.040404%	0.022050%	0.189900%	gnomAD	South Asian
155	*BRCA2*	c.7007G>A p.R2336H	Missense	P	3	0.69	0.060606%	0.000000%	0.000000%	gnomAD	
156	*BRCA2*	c.7072T>C p.S2358P	Missense	VUS	1	0.23	0.020202%	0.000797%	0.006550%	gnomAD	South Asian
157	*BRCA2*	c.7227T>C p.P2409P	Synonymous	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
158	*BRCA2*	c.7435+10G>A	Intronic	VUS	1	0.23	0.020202%	0.000400%	0.000887%	gnomAD	European (non-Finnish)
159	*BRCA2*	c.7436-1G>C	Intronic	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
160	*BRCA2*	c.7472A>T p.Q2491L	Missense	VUS	5	1.15	0.101010%	0.000000%	0.000000%	gnomAD	
161	*BRCA2*	c.7522G>A p.G2508S	Missense	VUS	1	0.23	0.020202%	0.015910%	0.225500%	gnomAD	East Asian
162	*BRCA2*	c.7544C>T p.T2515I	Missense	VUS	2	0.46	0.040404%	0.059780%	0.166200%	gnomAD	European
163	*BRCA2*	c.7633G>A p.V2545I	Missense	P	1	0.23	0.020202%	0.000709%	0.004020%	gnomAD	African/ African-American
164	*BRCA2*	c.7645T>G p.C2549G	Missense	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
165	*BRCA2*	c.4169delT p.L1390fs*20	Frameshift	P	6	1.38	0.121212%	0.000000%	0.000000%	gnomAD	
166	*BRCA2*	c.7700A>G p.Y2567C	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
167	*BRCA2*	c.771_775del p.N257Kfs*17	Frameshift	P	1	0.23	0.020202%	0.000798%	0.009244%	gnomAD	European (Finnish)
168	*BRCA2*	c.7766C>T p.P2589L	Missense	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
169	*BRCA2*	c.7783G>T p.A2595S	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
170	*BRCA2*	c.7855T>C p.W2619R	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	

171	*BRCA2*	c.7976G>A p.R2659K	Missense	P	2	0.46	0.040404%	0.000398%	0.000881%	gnomAD	European (non-Finnish)
172	*BRCA2*	c.8020_8021dupAA p.I2675fs*2	Frameshift	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
173	*BRCA2*	c.8021A>G p.K2674R	Missense	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
174	*BRCA2*	c.8092G>A p.A2698T	Missense	VUS	2	0.46	0.040404%	0.003537%	0.024030%	gnomAD	African/ African-American
175	*BRCA2*	c.8117A>G p.N2706S	Missense	VUS	1	0.23	0.020202%	0.006719%	0.052260%	gnomAD	South Asian
176	*BRCA2*	c.8155A>G p.I2719V	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
177	*BRCA2*	c.8322-47G>T	Intronic	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
178	*BRCA2*	c.8324T>G p.M2775R	Missense	VUS	1	0.23	0.020202%	0.003184%	0.006481%	gnomAD	European (non-Finnish)
179	*BRCA2*	c.8359C>T p.R2787C	Missense	VUS	1	0.23	0.020202%	0.000398%	0.002891%	gnomAD	Latino/ Admixed American
180	*BRCA2*	c.8395delA p.R2799Dfs*22	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
181	*BRCA2*	c.8452G>A p.V2818I	Missense	VUS	2	0.46	0.040404%	0.000398%	0.000880%	gnomAD	European (non-Finnish)
182	*BRCA2*	c.8478C>A p.Y2826*	Nonsense	P	4	0.92	0.080808%	0.000398%	0.003267%	gnomAD	South Asian
183	*BRCA2*	c.8487+39T>C	Intronic	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
184	*BRCA2*	c.8649A>G p.P2883P	Synonymous	VUS	2	0.46	0.040404%	0.000000%	0.000000%	gnomAD	
185	*BRCA2*	c.8878C>T p.Q2960*	Nonsense	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
186	*BRCA2*	c.67+1G>A	Intronic	P	6	1.38	0.121212%	0.000000%	0.000000%	gnomAD	
187	*BRCA2*	c.8930delA p.Y2977Ffs*11	Frameshift	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
188	*BRCA2*	c.8940delA p.E2981Kfs*7	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
189	*BRCA2*	c.8953+80G>A	Intronic	VUS	1	0.23	0.020202%	0.012700%	0.025900%	gnomAD	European (non-Finnish)
190	*BRCA2*	c.9038C>T p.T3013I	Missense	VUS	1	0.23	0.020202%	0.024480%	0.047480%	gnomAD	European (non-Finnish)
191	*BRCA2*	c.9052_9057delAGTAAA p.K3019_3020del	Inframe del	LP	3	0.69	0.060606%	0.003548%	0.032120%	gnomAD	African/ African-American
192	*BRCA2*	c.8881G>A p.G2961S	Missense	VUS	6	1.38	0.121212%	0.000000%	0.000000%	gnomAD	
193	*BRCA2*	c.9253del p.T3085Qfs*19	Frameshift	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
194	*BRCA2*	c.9317G>A p.W3106*	Nonsense	P	5	1.15	0.101010%	0.000000%	0.000000%	gnomAD	
195	*BRCA2*	c.9370_9381delAACCTCCA GTGG p.N3124_W3127del	Inframe del	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
196	*BRCA2*	c.9370_9383delAAC CTCCAGTGGCGinsCT p.R3128delinsL	Missense	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
197	*BRCA2*	c.9382C>T p.R3128*	Nonsense	P	1	0.23	0.020202%	0.002122%	0.020030%	gnomAD	African/ African-American
198	*BRCA2*	c.9397_9398delTC p.S3133fs*16	Frameshift	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
199	*BRCA2*	c.9501+4A>G	Intronic	VUS	2	0.46	0.040404%	0.001195%	0.016360%	gnomAD	Other
200	*BRCA2*	c.9502-12T>G	Intronic	VUS	1	0.23	0.020202%	0.010620%	0.027750%	gnomAD	Other
201	*BRCA2*	c.9556G>C p.A3186P	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
202	*BRCA2*	c.9586A>G p.K3196E	Missense	P	1	0.23	0.020202%	0.009546%	0.028220%	gnomAD	Latino/ Admixed American

203	*BRCA2*	c.9613_9614delGCinsCT p.A3205L	Missense	LP	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
204	*BRCA2*	c.9682delA p.S3228Vfs*21	Frameshift	P	1	0.23	0.020202%	0.000400%	0.000883%	gnomAD	European (non-Finnish)
205	*BRCA2*	c.9717G>A p.W3106*	Nonsense	P	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
206	*BRCA2*	c.9730G>T p.V3244F	Missense	VUS	1	0.23	0.020202%	0.001194%	0.010880%	gnomAD	East Asian
207	*BRCA2*	c.9772G>A p.E3258K	Missense	VUS	1	0.23	0.020202%	0.000000%	0.000000%	gnomAD	
208	*BRCA2*	c.9839C>A p.P3280H	Missense	P	2	0.46	0.040404%	0.001592%	0.016310%	gnomAD	Other
209	*BRCA2*	c.9934A>G p.I3312V	Missense	VUS	3	0.69	0.060606%	0.001592%	0.016300%	gnomAD	Other
210	*BRCA2*	c.9976A>T p.K3326*	Nonsense	LP	2	0.46	0.040404%	0.646800%	1.091000%	gnomAD	European (Finnish)

ACMG Class.: ACMG (American College of Medical Genetics and Genomics) Classification; Freq.: frequency, gnomAD: The Genome Aggregation Database; P: pathogenic; LP: likely pathogenic; VUS: variant of uncertain significance

Case Report

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Ductal Carcinoma *In Situ* Arising in Sentinel Axillary Lymph Nodes Excised From Patients With Breast Carcinoma - A Potential Diagnostic Pitfall. Report of Two Cases

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ABSTRACT

We present two cases of ductal carcinoma *in situ* (DCIS) that arose in axillary lymph nodes excised as the sentinel lymph node from two patients with breast carcinoma. The patient ages were 72 and 36 years and both patients underwent mastectomy and axillary lymph node dissection. In addition to DCIS in the sentinel lymph node, the first patient had a wide DCIS and microinvasion in the ipsilateral breast and a micrometastasis in another sentinel lymph node. The second patient was operated on after neoadjuvant chemotherapy and had DCIS and a small focus of invasion, in addition to invasive and *in situ* ductal carcinoma in the lymph node having signs of chemotherapy-induced regression. The presence of DCIS was confirmed by use of the immunohistochemical method with antibodies against myoepithelial cells. As a potential source of cellular origin, DCIS was accompanied by benign epithelial cell clusters in the lymph node in both cases. Morphologic and immunohistochemical features were similar in breast and lymph node neoplasms. We conclude that DCIS may rarely develop from benign epithelial inclusions in the axillary lymph node and is a potential diagnostic pitfall in cases having ipsilateral breast carcinoma.

Keywords: Breast; lymph node; ductal carcinoma *in situ*

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Key Points

- Ductal carcinoma *in situ* (DCIS) can develop from axillary lymph nodes.
- Pathologist should be aware of this rare situation to avoid misdiagnosis of metastasis because DCIS in the axillary lymph node is usually accompanied by ipsilateral breast carcinoma.

Introduction

The presence of benign epithelial inclusion (BEI) in the axillary lymph node is rare and its etiology is unclear (1-4). BEI in an axillary lymph node is often accompanied by ipsilateral benign or malignant breast diseases (4). Therefore, BEI in the axillary lymph nodes of patients with breast cancer can lead to false-positive diagnosis of metastatic disease (5). Similar to breast tissue, proliferative changes and atypia in epithelial cells have been reported in BEI in axillary lymph nodes (4). Ductal carcinoma *in situ* (DCIS) that developed within BEIs in an axillary lymph node has been reported in some cases where papillary lesions were present in the breast (6, 7). Furthermore, there are very few reports of DCIS that arose within BEIs in axillary lymph nodes that were not associated with the papillary lesions in the breast (8-10). The common feature of these cases is that only DCIS is detected in the breast.

Here we present two cases of DCIS encountered in a sentinel lymph node within BEIs occurring simultaneously with DCIS, microinvasive, and invasive carcinoma of the ipsilateral breast. We discuss the morphologic and immunohistochemical features, potential etiology and diagnostic significance.

Case Reports

Case 1: A 72-year-old female complained of a lump in her left breast. The lesion was palpable on physical examination. A digital mammogram showed an irregular, dense lump with pleomorphic calcifications. Sonographic examination confirmed the presence of irregular, hypoechoic tumor. An fluorodeoxyglucose (FDG)-positron emission tomography (PET) was also performed, which showed a left breast tumor maximum standardized uptake value (SUV_{max} 4.1) and minimal involvement in left axillary lymph nodes (SUV_{max} 1.4). A core biopsy of the breast lump was performed, and histopathological

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examination resulted in a diagnosis of high-grade DCIS with suspicion of microinvasion. On immunohistochemical examination, the neoplastic cells of the DCIS were negative for estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor-2 (HER-2), but positive for androgen receptor (AR).

The patient underwent a left mastectomy and sentinel lymph node (SLN) biopsy. An intraoperative pathologic examination using imprint cytology was performed in which two SLNs revealed metastasis, resulting in the completion of left axillary lymph node dissection. Grossly, the left mastectomy specimen contained an irregular tumor with firm to hard consistency and gray-white color, located in the upper lateral quadrant. The axillary dissection contained 13 grossly normal lymph nodes. The SLN biopsy specimen was composed of two lymph nodes, of which the largest one measured 1.2 cm, and they both partly stained with isosulphan blue dye. Both ER and PgR were negative in the DCIS and microinvasive carcinoma. One of SLNs contained a micrometastasis with two foci, of which the largest one measured 1.2 mm. Interestingly, the other SLN was extensively involved by a tumor displaying cribriform structures, reminiscent of the DCIS in the mastectomy specimen (Figure 1). Microscopic examination of the breast lump was reported as a high-grade DCIS with two foci of microinvasion, of which the largest measured 0.7 mm (Figure 2A, B). Additionally, an epithelial cell cluster, formed of squamoid cells, was observed beneath the capsule of the SLN. The cribriform structures in the SLN were formed of moderately atypical epithelial cells and contained an intact myoepithelial cell layer, which was evident even during examination of the slides stained with standard hematoxylin-eosin (Figure 2C, D). The presence of myoepithelial cells at the periphery of the cribriform structures of the SLN was confirmed with positive immunostaining with p63 (Figure 2E) and cytokeratin 14 (Figure 2F). Serial sectioning showed no sign of invasion in this SLN, and a diagnosis of DCIS arising in the lymph node was established. The neoplastic cells were negative for ER and PgR and positive for AR, similar to the DCIS from the left breast. The rest of the lymph nodes in the axillary dissection were free of tumor.

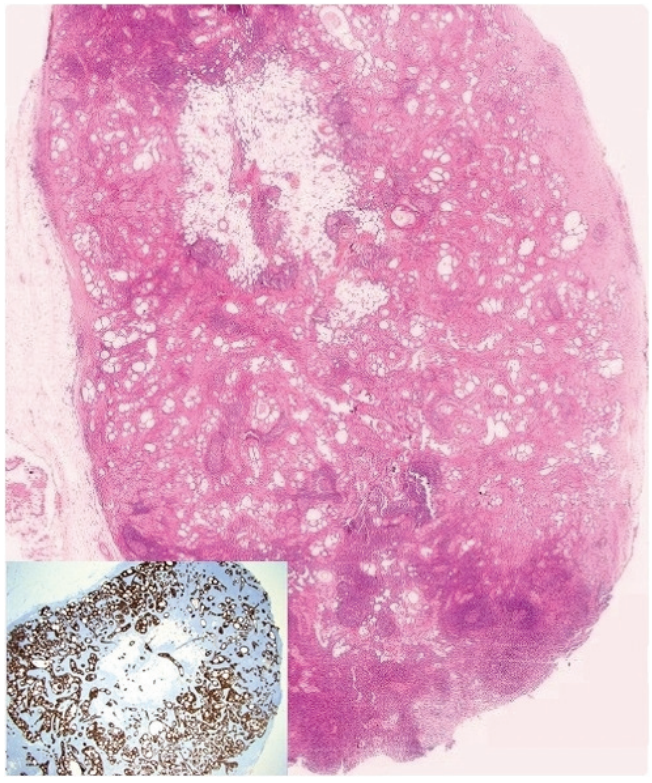

Figure 1. Extensive *in situ* ductal carcinoma in sentinel lymph node, and immunostaining by pancytokeratin (inset), (hematoxylin-eosin, x2; pancytokeratin, x40) (inset)

Case 2: A 36-year-old female suffered from a lump in her right breast and nipple discharge. A sonographic examination showed an irregular, hypoechoic mass with microcalcifications that measured 33 mm. Magnetic resonance imaging analysis showed heterogeneously contrasted right breast lesion that measured 47 mm. A F-18-PET (FDG-PET) analysis also revealed a tumor in the right breast (SUV_{max} 9.0), that measured 37 mm and right axillary lymphadenomegaly (LAM) (SUV_{max} 3.1) measuring 15 mm. Fine needle aspiration from the LAM was not diagnostic, but microscopic examination of a core biopsy of the right breast lump established a diagnosis of invasive carcinoma of no specific type. An immunohistochemical examination revealed that the neoplastic cells were positive for ER and PgR and negative for HER-2, and the Ki-67 proliferation rate was 15%. Following neoadjuvant chemotherapy (Doxorubicin/Cyclophosphamide, Paclytaxel), the patient underwent a right mastectomy and right axillary dissection after an intraoperative histopathological diagnosis of metastasis in the right axillary SLN.

During gross examination of the mastectomy specimen, a mass of 2.5 cm with firm to hard consistency and yellowish-gray colour was observed. The SLN biopsy specimen contained two lymph nodes, the largest of which measured 1.6 cm. The axillary dissection specimen contained 16 lymph nodes. Microscopic examination of the breast lesion revealed a 2.5 cm DCIS and a 1.5 mm invasive carcinoma.

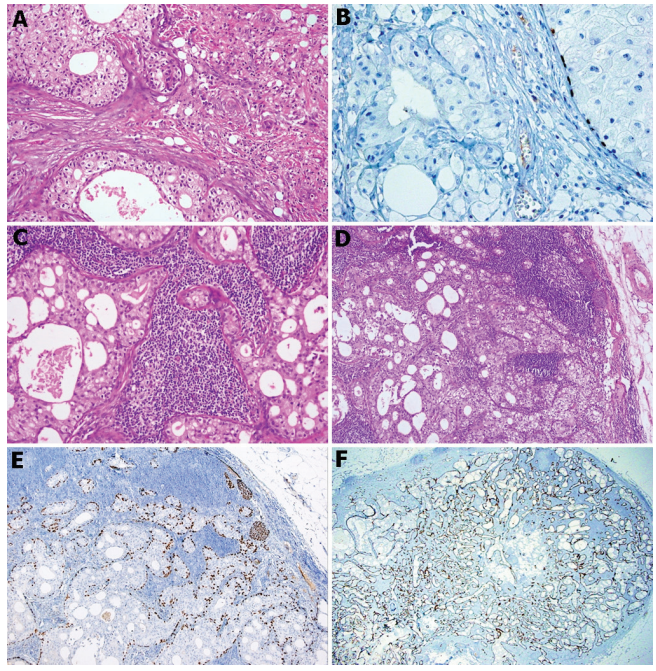

Figure 2A. High grade ductal carcinoma *in situ* with microinvasion in the breast, **B.** Ductal carcinoma *in situ* with immunoreactivity for p63, **C.** Ductal carcinoma *in situ* in the sentinel lymph node, **D.** Squamous inclusions and ductal carcinoma *in situ* in the sentinel lymph node, **E.** Immunohistochemistry for p63 shows a myoepithelial layer around the islands of epithelial cells, and squamous inclusions, **F.** Ductal carcinoma *in situ* with immunoreactivity for cytokeratin 14 (A: hematoxylin-eosin, x200; B: p63, x400; C: hematoxylin-eosin, x200; D: hematoxylin-eosin, x100; E: p63, x100; F: cytokeratin 14, x40)

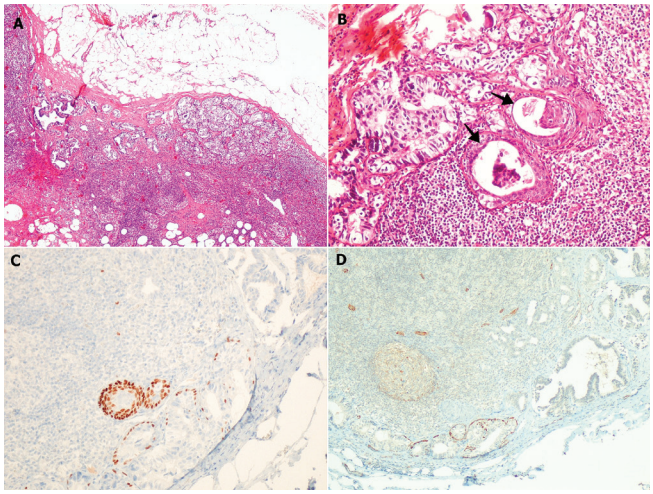

Figure 3A. Infiltrative metastatic carcinoma, and ductal carcinoma *in situ* in the sentinel lymph node, **B.** Ductal carcinoma *in situ*, and benign epithelial inclusion of skin adnexa-type (acrosyringeal) (arrows), **C.** Ductal carcinoma *in situ* and inclusions with immunoreactivity for p63, **D.** Ductal carcinoma *in situ* with immunoreactivity for smooth muscle myosin (A: hematoxylin-eosin, x100; B: hematoxylin-eosin, x200; C: p63, x200; D: smooth muscle myosin, x200)

Although the entire lesion was sampled, broad areas of fibrosis, suggestive of regression due to neoadjuvant chemotherapy were not detected, but only scattered foci within the DCIS-involved breast tissue. One of the SLNs contained metastatic carcinoma. However, on detailed microscopic examination, a microscopic focus of DCIS within the SLN, in addition to infiltrative metastatic carcinoma, and a microscopic focus of BEI of skin adnexa-type, and an area of fibrosis suggestive of tumor regression due to neoadjuvant chemotherapy (Figure 3A, B) were reported. The DCIS within the SLN was formed by cribriform structures containing an intact myoepithelial cell layer that stained positive for p63 (Figure 3C), smooth muscle myosin (SMM) (Figure 3D), and cytokeratin 14 on immunohistochemical examination. The neoplastic cells of the DCIS and infiltrative carcinoma within the SLN were similar in terms of nuclear size and atypia. The rest of the lymph nodes were free of metastasis.

Discussion and Conclusion

BEIs can occur in many anatomic sites, such as axilla, pelvis, and mediastinum (4, 11, 12). In axillary lymph nodes, BEIs include glandular inclusions (mammary-type and Mullerian-type), squamous inclusions, and mixed glandular-squamous inclusions (4). Since BEIs are associated with various breast diseases, they can pose a potential diagnostic pitfall in cases of metastatic carcinoma.

BEIs in the axillary lymph node may exhibit proliferative changes similar to breast tissue (6, 13). Furthermore, neoplastic change/alteration is also possible. In the literature, few cases of BEI-related DCIS in the axillary lymph nodes have been reported, accompanied by papillary lesions in lymph node and breast (6, 7). Additionally, there have been three reported cases of DCIS involving non-papillary BEI in the axillary lymph nodes (8-10). In all of these cases, only DCIS was detected in the breast tissue. In the two cases presented, there was BEI-related DCIS that was not accompanied by a papillary lesion. In contrast to previous reports, the presented cases demonstrated invasive carcinoma of the breast, as well as diffuse DCIS.

The presence of BEIs in axillary lymph nodes is often associated with implantation/displacement, metaplasia, or embryonic rests (7). In some studies, mechanical transport has been described as an alternative reason for the presence of epithelial cells in axillary lymph nodes (14, 15). It is known that mechanical transport is usually detected in papillary lesions and in the cases where a history of surgical manipulation of breast lesion has occurred (15). Morphologically, it presents as epithelial cells located in the subcapsular sinus, accompanied by erythrocytes and hemosiderin-laden macrophages (14). However, this etiologic reason does not explain well-organized BEIs nor DCIS in lymph node (6, 15).

It is assumed that DCIS develops in a BEI due to the presence of a separate benign glandular structure within the same lymph node (8). In the gynecological system, involvement of pelvic lymph node by a borderline tumor of ovarian type is also explained by the exposure of the ovary and lymph nodes to the same carcinogenic effects (16). The etiology of DCIS development from epithelial cells in the axillary lymph node is unclear. Nevertheless, we suggest that these cells in the lymph node have been exposed to the same carcinogenic effect as epithelial cells in the breast (8, 9). In support of this hypothesis, in a few reported cases, DCIS morphology in both lymph node and breast has been shown to be similar (8-10). Srinivasan et al. (8) and Commander et al. (10) demonstrated similar positivity for ER in the DCIS in both breast and the lymph node. We also detected similar morphologic and immunohistochemical features in the DCIS in both the breast lesion and the lymph node in one of the cases.

In contrast to earlier cases with small foci of DCIS in the axillary lymph node, a striking feature in one of the presented cases was that the lymph node that measured 1.2 cm was entirely involved by DCIS. Although it may be supposed that there is a ductus system in the lymph node, as in the breast tissue, there is no theoretical development of the ductus system in the lymph node. However, ductus-like structures filled with neoplastic cells, and development of stroma have been described and defined as "neoductgenesis" in breast tissue (17). It has been reported that this structuring is associated with cases of widespread neoplasia (18). The widespread involvement of lymph node by DCIS in our case, may be explained with this "neoductgenesis" theory.

Retrograde differentiation refers to the phenomenon where cancer cells that have already metastasized can revert to a less aggressive state. The hypothesis suggests that these cells may form structures like the myoepithelial layer. However, the literature lacks sufficient data on this subject. It is important to note that further research is required to gain a better understanding of retrograde differentiation and other potential mechanisms.

While BEIs are potential diagnostic pitfall areas, the presence of atypia and proliferative changes in epithelial cells makes the situation more complicated. Misinterpretation of the presence of DCIS in the lymph node could significantly affect clinical management. Indeed, BEI-related DCIS detected in the lymph node does not mean metastasis. Moreover, histopathologists dealing with breast carcinoma cases are aware that true metastases, morphologically mimicking DCIS, are common in axillary lymph nodes (19). To differentiate DCIS from true metastasis, it is helpful to perform immunohistochemical investigations to identify the myoepithelial cells, as is usually done in breast neoplasms. DCIS may be overlooked when there is a large invasive tumor area in the lymph node. As in our case, if the patient has received neoadjuvant chemotherapy treatment, the chance of DCIS being found in the lymph node increases. In other words, regression of the invasive tumor with chemotherapy makes the DCIS evident.

In conclusion, DCIS can develop in axillary lymph nodes. Pathologist should be aware of this rare situation to avoid misdiagnosis of metastasis because DCIS in the axillary lymph node is usually accompanied by ipsilateral breast carcinoma.

Informed Consent: Not necessary.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.T.; Concept: S.Ö., E.Y.; Design: A.B., S.Ö., E.Y.; Data Collection and/or Processing: A.B.; Analysis or Interpretation: A.B., S.Ö., E.Y.; Literature Search: A.Y.A., S.B.; Writing: A.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Case Report

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Breast Hematoma: A Rare Complication of Anticoagulant and Antiplatelet Use and Review of the Literature

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ABSTRACT

Oral anticoagulants and anti-platelet therapies are used for treatment and especially prophylaxis in clinical situations where there is a risk of thromboembolism or when thromboembolic events occur. The presented case was a patient who was hospitalized due to cellulitis in the leg, and was diagnosed with heart failure, obesity and chronic obstructive pulmonary disease. She was started on prophylactic oral anticoagulants for deep vein thrombosis and pulmonary emboli and subsequently developed spontaneous breast hematoma. The usual sites of such bleeding are the skin, gastrointestinal tract, genitourinary tract, central nervous system, retroperitoneum, muscle, and the site of recent surgical procedures or trauma while breast hematomas are usually of traumatic origin. Spontaneous bleeding into the breast after anticoagulant use is rare. While using anticoagulants, it should be kept in mind that, rarely, bleeding may occur in the breast. We advise that intervention in such cases is unnecessary, no matter how large the breast hematoma is, and that new anti-coagulant drugs may be safer.

Keywords: Breast hematoma; oral anticoagulant; treatment

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Key Points

- Although very rare, hematoma due to oral anticoagulants can also be observed in the breast. Breast hematomas can be managed with supportive treatment without any intervention.

Introduction

Anticoagulant therapy prevents the formation of new thrombi and thus the expansion of existing thrombi. Anticoagulant drugs include standard (unfractionated) heparin, low molecular weight heparin, direct-acting oral anticoagulants (DOAC), fondaparinux, danaparoid and vitamin K antagonists. Among the vitamin K antagonists, the most widely used drug is warfarin sodium. Oral anticoagulants inhibit prothrombin, a vitamin K-dependent coagulation factor produced in the liver, mainly by preventing the last step of the synthesis of factors 7, 9 and 10 (1). A common complication of oral anticoagulants is that they cause spontaneous bleeding. Spontaneous bleeding into the breast after anticoagulant use is rare (2). Breast hematoma may be asymptomatic or may present with swelling, pain or, as in the following case, initial swelling and extensive ecchymosis in the ongoing process (2-9).

Case Presentation

An 81-year-old female patient was admitted to the dermatology clinic due to cellulitis in the left leg (Figure 1). The patient was transferred to the Department of Pulmonary Medicine due to lung problems, including pleural effusion, tachypnea and low oxygen saturation. Warfarin (5 mg/day) was started prophylactically for deep vein thrombosis (DVT) and pulmonary embolism in the patient who had a diagnosis of heart failure, chronic obstructive pulmonary disease and obesity.

A general surgical consultation was requested because of complaints of swelling, pain and widespread ecchymosis that were more prominent in the left breast on the eighth day of hospitalization (Figure 2).

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On physical examination, hypotension (88/57 mmHg.) and tachycardia (117/min.) were present with a body temperature of 36.7 oC. There was swelling and widespread ecchymosis in the left breast, while the ecchymosis of the right breast was relatively more limited. In addition, there was widespread ecchymosis of the left lateral abdomen (Figure 2,3). High international normalized ratio (INR) of 2.23 (Normal range [NR] = 1.0), prolonged activated partial thromboplastic clotting time (APTT) of 41 seconds (NR 21-35 seconds) and prothrombin time of 26.6 seconds (NR 10-13 seconds) were found during coagulation assessment. White blood cells and platelets were within normal limits, but on 24-hour hemogram follow-up, hemoglobin decreased from 13.6 g/dL to 8.1 g/dL, and hematocrit fell from 42.1% to 24.6%.

On breast ultrasonography (USG), the left breast skin was subcutaneously thickened and linear fluid loculations were observed between the left breast fat lobules. No solid mass that could cause hematoma was detected on initial USG. Since it may cause pain or bleeding in the breast in acute phase, the patient was recalled for follow-up after discharge when repeat USG and mammography were planned. These imaging studies, performed six weeks later, revealed a deep-seated collection area of up to 3 cm in the thickest part of the left breast. No finding suggestive of malignancy was observed (Figure 4).

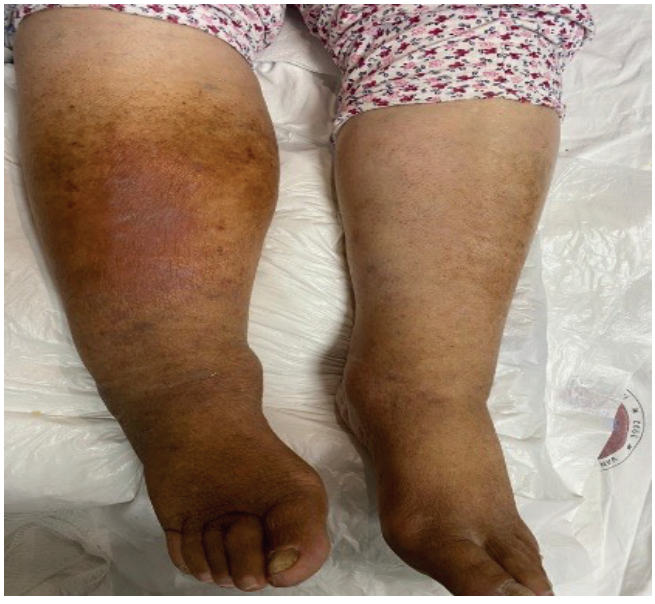

Figure 1. The patient with cellulitis in the right leg was hospitalized

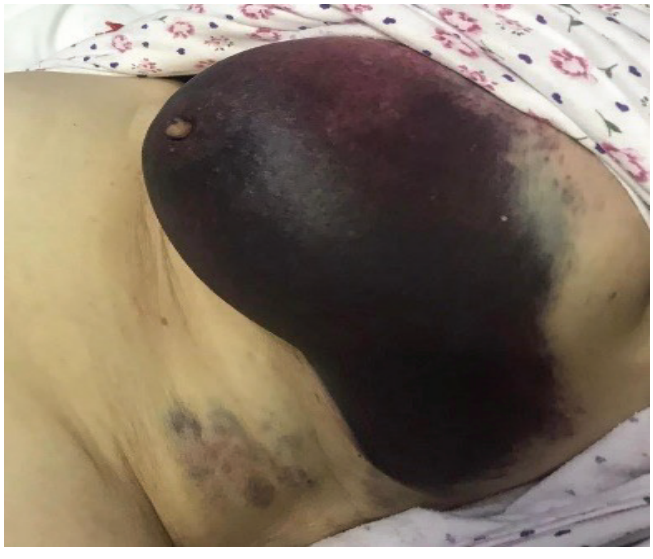

Figure 2. Left breast hematoma. The appearance of the patient at first examination

Treatment

Anticoagulants were discontinued as soon as breast hematoma was detected. We found that the patient did not pay attention to the drug doses and the follow-up was not well done. The patient was evaluated by the hematology department and low molecular weight heparin was started. Oral anticoagulant treatment of the patient was stopped. Vitamin K and vitamin C supplements were given. Due to the risk of embolism, low molecular weight heparin treatment was continued as recommended by the relevant departments. A tight bandage was applied. The patient was given two units of fresh frozen plasma and 10 mg of phytomenadione. In addition, due to the low hemoglobin levels and symptoms, she was also given two units of erythrocyte suspension. After transfusion, the hemoglobin value was 10.2 gr/dL. Approximately 48 hours after the patient's oral anti-coagulant treatment was discontinued, the INR value decreased below 2. Afterwards, the patient was started on LMWH treatment. Hemoglobin levels and INR checks were made during follow-up. It was observed that the INR value fell

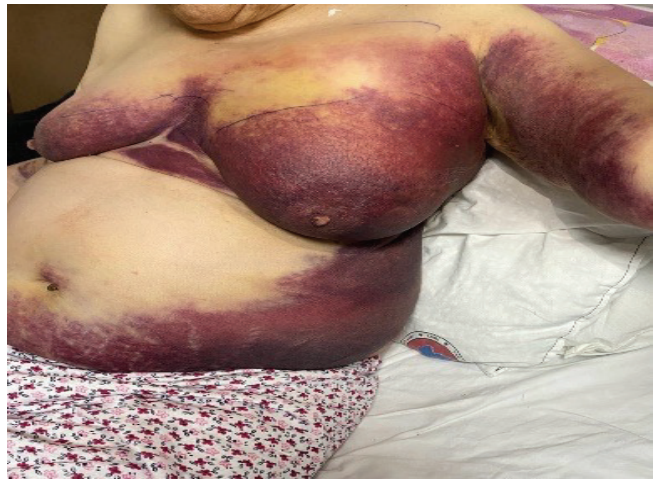

Figure 3. The image of the patient three days after the first examination

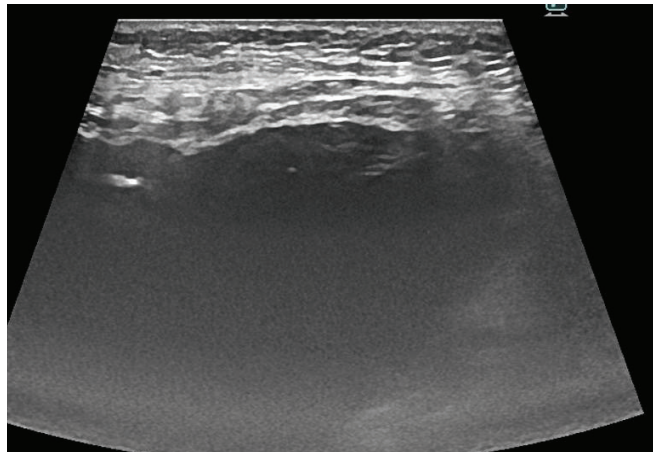

Figure 4. Breast USG image of the patient at the six week follow-up

below 2 48 hours after warfarin was discontinued, and the INR value taken 96 hours later returned to the normal range. After the eryrocyte suspension was given to the patient, it was observed that there was no decrease in the hemogram as a result of the complete blood count taken every other day. Furthermore, regression was observed in the ecchymosis areas and she was discharged with a plan to reassess after six weeks. At the six-week follow-up the areas of ecchymosis areas were observed to have improved (Figure 5) and her blood count was found to be within normal values.

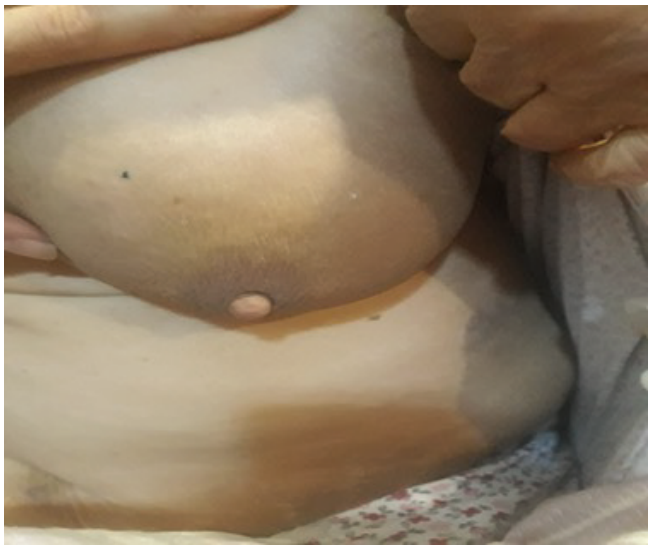

Figure 5. The patient at the six week examination

Discussion and Conclusion

Initiating oral anticoagulants therapeutically or prophylactically can lead to life-threatening bleeding in some patients as a result of their narrow therapeutic range, despite their antithrombotic benefits. In prospective, randomized, placebo-controlled studies in patients with DVT and stable pulmonary thromboendarterectomy (PTE) it was shown that oral rivaroxaban and apixaban were as effective as standard treatment in terms of recurrence and early mortality in the acute phase of venous thromboembolism (VTE), and cause less major bleeding compared to warfarin in long-term maintenance treatment (10, 11). In placebo-controlled studies comparing dabigatran and warfarin, it was reported that dabigatran was as effective as warfarin in prolonged treatment (11). There is strong evidence that new oral anticoagulants, such as rivaroxaban, dabigatran, apixaban, edoxaban, can be used as an alternative to warfarin, which we have used so far in the long-term treatment process (12, 13). Due to the fact that new generation anticoagulants are safer, there is increasing interest in the use of these new new drugs around the world. These hemorrhages occur mainly in the gastrointestinal tract, kidney, and from ulcerated mucosa. However, it should be remembered that bleeding may occur in any organ, such as the breast, which is a possible site of trauma. Spontaneous breast hematoma is a very rare clinical entity in patients receiving anticoagulant therapy and those with hematological disease, and few cases have been reported in the literature to date (2-9). Thrombocytopenia, coagulation disorders or a history of anticoagulant therapy should be investigated in these patients (3). In general, the appropriate management of anticoagulant therapy for the elderly is a therapeutic challenge (7). When planning treatment, the benefits must outweigh the risks and complications. In order to reduce the risk of bleeding and maximize safety in this patient group, a parameter to be considered before starting anticoagulant therapy is the appropriate evaluation of renal function (7). The risk of bleeding increases in patients with renal failure or dysfunction (7).

Repeat imaging is mandatory until complete clinical and imaging resolution of the hematoma has been recorded (9). If the hematoma does not resolve completely and a residual mass or mammographic abnormality persists, further investigations, including biopsy, are recommended to rule out an underlying malignancy (7). Although surgical drainage and packing and aspiration of the hematoma are performed in some cases (3, 7, 9), we believe that the treatment of breast hematomas caused by anticoagulation should be mainly conservative, including reversal of possible excessive anticoagulation, with the proviso that these hematomas should be followed closely. No surgical or invasive approach to the breast should be made until the bleeding parameters are stabilized. However, imaging should be performed, given the possibility that these hematomas may be cystic breast tumors. No cystic or solid mass was detected on USG in the presented case. At six week follow-up, imaging studies including USG and mammography demonstrated that the hematoma was completely resolved and no findings suggestive of malignancy were detected.

Among the complications that may occur in spontaneous breast hematomas, hematoma infection (7) and necrosis (4, 5) have been reported. Such necrosis is a serious complication and mastectomy may be required (4).

As is evident from the presented case and literature reports, spontaneous breast hematomas require careful investigation and follow-up.

Conclusion

It has been shown that DOACs are at least as effective as warfarin and are safer in terms of bleeding in long-term and prolonged anticoagulant therapy. Thus DOACs may be preferred in patients whose INR is difficult to control therapeutically but who are hemodynamically stable. Even in cases of severe breast hematoma, close follow-up may be sufficient. We suggest that avoiding any intervention is the most effective strategy, unless serious complications develop. Knowing and using new drugs can reduce such complications. However, if the hematoma does not resolve completely and a residual mass or mammographic abnormality persists, further investigation with biopsy is recommended to rule out an underlying malignancy.

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and/or Medical Practices: E.D., S.Ç.; Concept: E.D., S.Ç.; Design: E.D., S.Ç.; Data Collection and/or Processing: E.D., S.Ç.; Analysis and/or Interpretation: E.D., S.Ç.; Literature Search: E.D., S.Ç.; Writing: E.D., S.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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Letter to the Editor

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Advances in Artificial Intelligence and the Potential Impact on Oncoplastic Breast Surgery

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Cite this article as: Akalın Ç. Advances in Artificial Intelligence and the Potential Impact on Oncoplastic Breast Surgery. Eur J Breast Health 2023; 19(3): 261

Dear Editor,

Oncoplastic breast surgery is a rapidly evolving field that combines the principles of oncologic surgery and plastic surgery to achieve optimal outcomes for breast cancer patients. By integrating techniques such as tumor resection, breast reconstruction, and symmetry procedures, oncoplastic surgery aims to minimize traditional breast cancer surgery's negative aesthetic and functional consequences while maintaining or even improving oncological outcomes.

Artificial intelligence (AI) can potentially revolutionize various aspects of medicine, including surgery. By employing advanced machine learning algorithms, AI can provide valuable insights and assistance to medical professionals in making more accurate diagnoses, formulating optimal treatment plans, and even predicting patient outcomes. It is, therefore, crucial that we explore the potential integration of AI advancements in the field of oncoplastic breast surgery.

Some possible areas of exploration include AI in preoperative planning, wherein algorithms analyze patient-specific anatomical data to predict optimal surgical approaches and individualized reconstructive techniques. Additionally, AI could be employed in intraoperative decision-making, with real-time imaging analysis guiding the surgeon to achieve more precise tumor resections and better cosmetic results. Furthermore, AI-driven postoperative monitoring could enable the early detection of complications or recurrences, allowing for timely interventions and improved patient care.

In conclusion, I kindly request that you consider the importance of this topic and encourage research and discussions related to the potential impact of AI advancements on oncoplastic breast surgery. By promoting this area of inquiry, we can foster innovation and ultimately improve the quality of care for breast cancer patients worldwide.

Sincerely,

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