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European Journal of Breast Health

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European Journal of Breast Health (Eur J Breast Health) is an international, open access, online-only periodical published in accordance with the principles of independent, unbiased, and double-blinded peer-review.

The journal is owned by Turkish Federation of Breast Diseases Societies and it is published quarterly on January, April, July, and October. The publication language of the journal is English. The target audience of the journal includes specialists and medical professionals in general surgery and breast diseases.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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Abstract: An English abstract should be submitted with all submissions except for Letters to the Editor. Submitting a Turkish abstract is not compulsory for international authors. The abstract of Original Articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

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Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

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Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or tatal of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

BI-RADS: Breast imaging, report and data systems

referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

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Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. References published in PubMed should have a PMID: xxxxxx at the end of it, which should be stated in paranthesis. The reference styles for different types of publications are presented in the following examples.

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

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.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

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.

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Review

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Reliable Biomarkers to Identify New and Recurrent Cancer

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ABSTRACT

Breast cancer is the most frequent cancer detected throughout both the developing and the developed world. Its incidence is on the rise in the developing world. Great strides have been made in developing biomarkers to guide therapy for women diagnosed with breast cancer. Far fewer advances have occurred with biomarker development for the early diagnosis of breast cancer. Standard screening for new and recurrent breast cancer involves clinical breast exam and breast imaging. There are no Food and Drug Administration (FDA) approved noninvasive body fluid tests for the early detection of new or recurrent breast cancer. Promising biomarker approaches include multianalyte testing of tissue for individuals diagnosed with breast cancer and body fluid analysis for both at risk women and to monitor individuals after treatment.

Keywords: Breast cancer, biomarkers, carbohydrates, proteins, lipids

Cite this article as: Sauter ER. Reliable Biomarkers to Identify New and Recurrent Cancer. Eur J Breast Health 2017; 13: 162-167.

Introduction

The breast is the most frequent site of cancer among women in both developed and in developing countries (1). Breast cancer is the most frequent cause of cancer death in women from less developed countries and second most frequent (after lung cancer) among women in developed countries (1). It is increasing in incidence in the developing world due to increased life expectancy, increased urbanization and the adoption of western lifestyles (2). According to the World Health Organization (WHO), "Early detection in order to improve breast cancer outcome and survival remains the cornerstone of breast cancer control" (2).

In 2017 approximately 41.070 U.S. women are projected to die from breast cancer (3). It is estimated that in 2011 508.000 women worldwide died of breast cancer (2). Although incidence rates are lower in developing regions than in Western Europe and North America, almost 50% of breast cancer cases and 58% of deaths occur in less developed countries (2). Breast cancer survival rates range from over 80% in many developed countries to below 40% in low-income countries (4). The low survival rates in less developed countries are due to later stage at disease presentation, as well as by the lack of adequate diagnosis and treatment facilities.

Early detection is crucial to improving the survival of individuals with breast cancer, as survival is inversely related to disease stage (5). An invasive needle or surgical biopsy must be performed when an area of suspicion is identified in order to confirm the presence of malignancy, and most of these invasive biopsies will turn out to be benign (6). The development of non-invasive biomarkers that would distinguish between women with or without breast cancer is highly desirable.

Twenty-one percent of all breast cancer deaths worldwide have been attributed to alcohol use, high body mass index (BMI), and physical inactivity (7). Thus, while some breast cancers may be prevented through lifestyle modification strategies, most cannot. Currently known risk factors address only a subset (up to half) of risk for breast cancer. Biomarkers hold promise to aid breast cancer assessment. A highly predictive biomarker is stable, reproducible, sensitive, specific and easy to detect. Biomarkers can be assessed in tissue and/or body fluids.

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Whereas tissue biomarkers are fine for women from whom breast tissue has been collected for diagnostic purposes, body fluid analysis is more desirable when evaluating healthy individuals.

Breast Cancer Markers in Clinical Use

Physical Examination

Breast self-examination (BSE) has not been shown to be an effective screening strategy, but does raise awareness of the disease and therefore is recommended by the WHO for this purpose (7). The U.S. Preventive Services Task Force (USPSTF) recommends against teaching BSE (8). The American Cancer Society (ACS) advises the use of BSE as an optional screening tool. The WHO suggests that CBE has been demonstrated effective both in affluent and less affluent countries, whereas the USPTF has concluded that current evidence is insufficient to determine if CBE adds additional benefit to screening mammography in women 40 years or older (7). The ACS does not recommend BSE or CBE for average risk women (9).

Breast Imaging

Mammography: The sensitivity of mammography is inversely related to breast density such that higher density decreases sensitivity. Anything that may increase breast density, such as fibrosis related to prior surgery and/or breast irradiation, decreases mammographic sensitivity. For average risk women, the USPSTF currently recommends biennial mammographic screening for women 50-74 years of age, indicating that the decision to begin mammography screening earlier than age 50 is an individual choice. The ACS recommends that women be given the opportunity to start annual mammographic screening at age 40, and that they should in any case start annual mammographic screening by age 45. Starting at age 55 women should be given the option to continue annual or transition to biannual screening. The ACS further indicates that women should continue mammographic screening so long as they are in good health and have a life expectancy of at least 10 years (9).

Ultrasound: In average risk women undergoing asymptomatic screening, ultrasound is generally used as a supplement for those with dense breast tissue. For women with a sign or symptom of breast disease, according to the American College of Radiology (ACR) Practice Guidelines (2016 revision), breast ultrasound is appropriate for 1) the evaluation and characterization of palpable masses and other breast related signs and/or symptoms; 2) evaluation of suspected or apparent abnormalities detected on other imaging studies, such as mammography or magnetic resonance imaging (MRI); 3) initial imaging evaluation of palpable masses in women under 30 years of age who are not at high risk for the development of breast cancer, and in lactating and pregnant women. 4) evaluation of problems associated with breast implants, 5) guidance for breast biopsy and other interventional procedures, 6) treatment planning for radiation therapy, and 7) identification of and biopsy guidance for abnormal axillary lymph nodes (10).

Magnetic Resonance Imaging: Breast MRI is not recommended as the initial tool to screen average risk woman except as part of a scientific study. Current indications for breast MRI based on American Society of Breast Surgeons 2017 recommendations include screening high risk patients, screening the contralateral breast in women newly diagnosed with breast cancer who have associated clinical or conventional indeterminate imaging findings suspicious for malignancy, assessing extent of disease in women with *in situ* or invasive carcinoma both before and after surgery, assessment for eligibility and respnse to neoadjuvant endocrine therapy or chemotherapy before, during, or after treatment, for evaluation of suspected breast implant rupture, and in assessing breast cancer recurrence when clinical, mammographic or ultrasound findings are inconclusive (11).

Biomarkers

There has been considerable effort to identify novel biomarkers that might offer clinical utility. Relatively few identified candidates have been subjected to rigorous validation. Validation requires the analysis of hundreds and sometimes thousands of samples to adequately survey the variability in biomarker expression that is present in patient samples.

The evaluation of changes in both DNA and proteins in body fluids and tissue shows considerable promise in the diagnosis and management of breast cancer, but analysis of body fluids is preferred for diagnosis because sampling is minimally invasive and ongoing assessment is practical. Analysis of fluids also has promise, either alone or in combination with tissue analysis, for determining if breast cancer will recur.

Despite the potential already demonstrated, researchers have not delivered validated biochemical markers that can be used to optimally diagnosis and manage breast cancer. Only four of the Food and Drug Administration (FDA)-approved markers (CA 15-3, CA 27.29, HER- 2/neu, and circulating tumor cells analysis of EpCAM, CD45, CK8, 18, 19) can be measured and assessed longitudinally. Notably, there are no FDA approved biomarkers for breast cancer diagnosis or screening (12).

Biomarkers in tissue

1. Hormone receptor status: Cancers that express the estrogen receptor (ER) are estrogen dependent, whereas cancers that do not express ER are estrogen independent. Two thirds of invasive breast cancers express ER and are classified ER+ (13). The progesterone receptor (PR) becomes activated when it interacts with the hormone progesterone. Approximately 65% of breast cancers that are ER positive are also PR positive. Expression of both ER and PR are measured via immunohistochemical (IHC) assay. Tumors that are ER+ and/or PR+ generally respond to antihormonal therapy with tamoxifen or an aromatase inhibitor, whereas those that are ER/PR negative do not.

2. Cytokeratin (CK): IHC expression of CK7, CK8, CK18 and CK19 is observed in more than 90% of all breast carcinomas (14). Expression of CK5/6, CK14 and CK20 correlate with high tumor grade.

3. Heregulin (HER)2: Also known as epidermal growth factor receptor (EGFR) II, HER2 is overexpressed in 20% of breast cancers, most often due to HER2 gene amplification (15). HER2 overexpression upregulates the cell signaling pathway leading to uncontrolled cell growth. HER2 positive breast cancers are generally aggressive and patients with HER2 overexpression have a worse prognosis than patients whose breast cancers do not overexpress HER2 (16). FDA approved agents targeting HER2 include transtuzumab, lapatinib, T-DM1 (adotrastuzumab emtansine) and pertuzumab.

4. Ki67: This protein is a marker of cell proliferation for many types of cancer. The fraction of cells that stain positive for this protein reflects the fraction of cells in G1, S, G2 or mitosis, but not those that are in G0. Higher levels of Ki-67 correlate with more rapid tumor growth and tumor aggressiveness (17).

5. Oncotype Dx: This is a 21 gene expression biomarker panel that uses formalin fixed tissue. The test is valid for women with hormone

sensitive breast cancer. It is most often used for women with early stage (DCIS, stages I and II node negative) disease. Results provide a statistical inference of chemotherapy benefit and likelihood of recurrence (18).

6. Mammaprint: This 70 gene biomarker panel uses fresh or fixed tissue to determine the likelihood of recurrence of breast cancer within 10 years of diagnosis and response to treatment with chemotherapy. Mammaprint can be used to analyze both ER (-) and ER+ early stage (i.e. stage I or II) node negative (U.S. criteria; international criteria allow up to three positive nodes) invasive cancers (19).

7. Prosigna: The 50 gene assay, formerly called the PAM50 test, analyzes the activity of certain genes in node-negative (stage I or II) or node positive (stage II), hormone receptor-positive breast cancer patients. It provides individualized assessment of a patient's risk of recurrence at 10 years if given endocrine therapy alone (20).

Biomarkers in body fluids

The most common body fluid currently in use for biomarker detection is blood or its components. Three breast specific fluids that are being evaluated for predictive biomarkers are nipple aspirate fluid (NAF), breast milk and ductal lavage (DL). Each fluid contains proteins, carbohydrates and lipids, DNA and RNA. NAF, collected neat through breast massage +/- suction on the breast nipple, has a relative paucity of cells, but concentrated proteins, carbohydrates and lipids. Breast milk contains high concentrations of certain proteins, including α-lactalbumin, lactoferrin, secretory IgA, lysozyme and albumin, whose primary function is feeding an infant, but there are also less abundant proteins, carbohydrates and lipids with potential cancer biomarker usefulness. DL is collected through the insertion of a micro catheter into the nipple, providing irrigating fluid, and analyzing the effluent. There are more cells in DL than NAF. The irrigant dilution factor for analysis of proteins, lipids and carbohydrates is somewhat uncertain, as often not all of the irrigant is collected.

Biomarkers in body fluids: serum

1. CA15-3 and CA 27.29: For women diagnosed with breast cancer, assessment of the expression of both CA 15-3 (MUC1) and CA 27.29 in serum are FDA approved to monitor patients. American Society of Clinical Oncology guidelines recommend using these tumor markers in conjunction with imaging and clinical examination to assess treatment response/failure. A confirmed increase of >= 25% has been suggested as clinically significant (21).

2. HER2/neu: Reports suggest that the sensitivity of HER2/neu tissue testing may be enhanced by evaluating the external fragment of the HER2 protein, which is shed into the bloodstream. This assessment is referred to as the serum HER2 (sHER2) test (22). An increasing level of circulating HER2 is an early indicator of progression, particularly in HER2-positive patients. The rise and fall parallels the clinical course of disease, independent of therapy. HER2 status of the primary tumor may not accurately reflect the HER2 status of recurrent disease. As such, elevated serum HER2 levels may be an early signal of a HER2-positive metastatic tumor and therefore alert the physician to re-assess HER2 status using a tissue test (22).

3. Circulating tumor cells (CTCs): The CellSearch system was FDA approved in 2004 to detect the presence of CTCs and monitoring diseas progression based on CTC level in patients with metastatic breast, colorectal, and prostate cancer. The CellSearch test has not yet been established as a means of selecting therapies for these patient populations, hampering its incorporation into treatment guidelines (23).

Breast Cancer Biomarkers Being Evaluated

Biomarkers in tissue

1. *p53* is the most commonly mutated gene in human cancers. Individuals who have germline mutations in *TP53* have Li-Fraumeni syndrome. Li-Fraumeni syndrome is rare, with approximately 400 known families. Patients with Li-Fraumeni syndrome are at high risk for early-onset breast cancer. The primary limitation of performing screening for germline p53 mutations is their rarity (24).

3. Ataxia Telangiectasia (AT) is caused by mutations in the AT mutated (*ATM*) gene which leads to the generation of defective AT protein (25). The normal AT protein detects DNA strand breaks, recruits proteins to fix the break, and prevents a cell from making new DNA until the repair is finished. People with AT are at an increased risk of multiple cancers, including lymphoma, leukemia, and breast cancer. Compared to the general population, women who are heterozygous or homozygous for AT have double the risk of developing breast cancer (26). The relative infrequency of the mutation limits its justification for screening the general population to identify individuals at increased risk.

4. Mutations in the Phosphatase and Tensin (*PTEN*) gene can contribute to the development of a variety of cancers, including breast cancer (26) Approximately 50% of breast cancers have loss of PTEN expression, which is associated with lymph node metastases and poor survival (27). Individuals with Cowden's disease, who have germline mutations in PTEN, have a 25-50% lifetime risk of developing breast cancer (28).

5. Multiple gene analyses: There are a variety of hereditary breast cancer syndromes which have genetic mutations associated with them, and confer an increased risk of developing breast +/- other malignancies (29). These include Hereditary Breast and Ovarian Cancer syndrome, with mutations in *BRCA1* or *BRCA2*, Li-Fraumeni, with mutations in *TP53*, Cowden's syndrome, involving *PTEN*, Hereditary Diffuse Gastric Cancer syndrome, involving *CDH1*, Peutz-Jeghers, involving *STK11*, Lynch syndrome, involving *MLH1*, *MSH2*, *MSH6*, or *PMS2*, and Fanconi anemia, involving *PALB2*. Lifetime risk of breast cancer is over 20% for mutation carriers of these syndromes, ranging up to 80% for *BRCA1* mutation carriers (29). Gene panels have been developed to evaluate patient samples for alterations in some or all of these genes.

a. BROCA: This panel from the University of Washington evaluates mutations in genes involved with a variety of human cancers. BROCA is most useful for analyzing patients with a suspected cancer predisposition. An advantage of the BROCA gene panel is that specific gene testing can be selected or the investigator can opt for the entire panel. The number of genes in the panel changes over time based on new information (30).

b. BreastNext: This 17 gene panel developed by Ambry Genetics is very similar to the BROCA panel in that it analyzes cancer risk and is best suited for patients with a suspected hereditary predisposition to breast or ovarian cancer. Like BROCA, this panel offers the option of specific gene testing or analysis of the entire panel. A further advantage to BreastNext is that it includes duplication and deletion gene analysis (30).

c. BRCAPLUS: This 6 gene panel developed by Ambry Genetics performs next generation sequencing (*BRCA1/2, CDH1, PALB2, PTEN, TP53*). Each of the genes analyzed is linked to hereditary cancer syndromes and has published management guidelines (31).

d. Breast/Ovarian cancer panel: This 20 gene panel developed by GeneDx evaluates genes that have been linked to an hereditary disposition to breast and/or ovarian cancer (30).

e. The Myriad myRisk® Hereditary Cancer test is a 28-gene panel that identifies an elevated risk for eight cancers (breast, ovarian, gastric, colorectal, pancreatic, melanoma, prostate, and endometrial) (30).

Gene panels have also been developed by Ambry Genetics, BreastHealthUK, Centogene, the Emory Genetics Laboratory, Fulgent Diagnositcs, Invitae, Quest Diagnostics, and Prevention Genetics (29).

Current Biomarker Challenges

The accurate assessment of biomarker expression is influenced by many things. Three of the most important factors are tumor heterogeneity, treatment effect, and whether the tumor is new or recurrent. Because of tumor heterogeneity, expression of tumor markers can differ in a patient with newly diagnosed, untreated breast cancer between core biopsy and surgical resection specimens. Additionally, treatment can lead to changes in expression, with resistant subclones which survive becoming predominant after treatment. Tumor DNA, which is inherently unstable, can change over time, leading to changes in primary vs. recurrent/persistent tumors. Moreover, some breast tumors contain both basal and luminal clones with distinct genetic alterations (32). The molecular phenotype of primary vs. recurrent tumors can differ due to treatment of the primary and the innate instability of tumor DNA.

Heterogeneous tumors

Immunohistochemical analysis of a newly diagnosed breast cancer generally includes ER, PR and HER2, and is most often performed on the core biopsy specimen. Because of intratumoral heterogeneity, the smaller the core biopsy, the more likely it is to not accurately represent the ER, PR or HER2 status of the entire tumor (33). Moreover, expression may differ between a primary and recurrent tumor as well as between the primary tumor and its metastasis/metastases (33).

There is heterogeneity in tumor cell division between diagnostic needle or core biopsy and surgical resection specimens as demonstrated in the proliferation marker Ki67. The authors propose this the average proliferation difference was 3.9%, with biopsy specimens having a higher proliferation rate than surgical excision specimens and with the assessment of 800 additional (total 1000) cells, the difference was no longer present. The authors proposed this was due to hot spot sampling in the core specimens. Treatment can also contribute to acquired heterogeneity because it can alter the tumor phenotype and change the ER/PR and HER2 status of the original tumor. These findings suggest that overall under sampling of the primary tumor may be occurring.

The effects of treatment

Both endocrine and chemotherapeutic cancer treatment can change tumor phenotype. Investigators evaluating postmenopausal women with ER+ breast cancer who were receiving neoadjuvant endocrine therapy found that the ER downregulator fulvestrant decreased Ki67, ER and PR expression after 16 weeks of treatment in a dose dependent fashion (34). In a separate study of women who received neoadjuvant chemotherapy for breast cancer, tumor grade changed in 35%, ER, PR and HER2 expression in 43, 55 and 27% of cases, respectively (35).

Whether the tumor is new or recurrent

Primary vs. recurrent tumors can differ both due to treatment of the primary and the inherent instability of tumor DNA. If recurrent disease is in a different location from the primary tumor, a particular alteration may have selected for tumor spread to the new location. In a study evaluating patients with biopsy proven relapsed breast cancer, using a similar approach to assess expression in both primary and relapsed specimens, the molecular phenotype of the original tumor and the tumor metastasis, there was 19% discordance in the ER/PR or HER2 status between the primary and relapsed lesion (36). A second study evaluating patients with biopsy proven relapsed/metastatic disease observed discordance for ER, PR and HER2 of 32, 41 and 15%, respectively (37). In the second study there was an overall survival advantage among women with stable ER+ tumors vs. those whose tumors changed to ER- at relapse.

Consequences of Current Biomarker Limitations

Standard screening for breast cancer involves physical examination and breast imaging, generally mammography with or without breast ultrasound. These tools alert the treating provider to the presence of a lesion which is palpated and/or an abnormality which is visualized. The diagnosis of breast cancer requires demonstration of visual changes in the nuclei in a cytologic or histologic preparation of breast cells. In order to obtain the cells for pathologic review, an invasive needle, core, or surgical biopsy must be performed. These procedures are subject to sampling error, and only approximately 15-20% of the procedures detect malignancy (38). Liquid biopsies have the goal of providing useful clinical information from body fluid analysis. These body fluids can be collected noninvasively, or minimally invasively. These body fluids can be either breast specific, such as nipple aspiration, ductal lavaga (DL), and ductoscopy, or not, such as blood.

Discovery Targets

The success of breast cancer biomarker research depends on: 1) combining newly discovered biomarkers with established methods so that cancer diagnosis can be optimized; 2) identifying biomarkers to establish response to treatment, recurrence, and survivorship; 3) the use of biomarkers to guide therapies in patient targeted medicine; and 4) the use of biomarkers to determine drug candidates for the development of new therapies (17).

There are no generally accepted body fluid biomarkers for the early detection of breast cancer. A major barrier to the development of early breast cancer detection biomarkers relates to disease heterogeneity. Biomarker studies to date have generally been small, evaluate one or a few markers in a single sample type, and enrollment and exclusion criteria vary from study to study. Some studies evaluate subjects at high risk for cancer, based on risk assessment or clinical findings, while other biomarker studies screen the general population. Finally, cancer detection biomarker studies often collect a single sample, which may not adequately account for random biomarker variation in a given individual. More progress has been made among subjects which biopsy proven breast cancer, since a patient's tumor can be phenotyped. Because of the inherent instability of tumor DNA, as well as treatment effect, changes in biomarkers can occur, as already discussed. Nonetheless, new biomarker development, both for the early detection and treatment of breast cancer, is an active area of investigation. Among the biomarkers under evaluation are autoantibodies, inflammatory response molecules, DNA methlyation (i.e. CpG Islands), benign breast disease, and pregnancy associated breast cancer biomarkers.

Challenges in the identification and validation of new biomarkers

Most biomarker development studies are not completely representative due to selection bias. Biomarker assessment in healthy individuals is generally limited to body fluids, as there is no tumor to collect and ethics boards are reluctant to approve invasive approaches in healthy individuals. Successful sample collection of some body fluids such as NAF or DL requires learning the technique and practice. Inadequate sample collection can limit biomarker assessment.

Validation of an initially promising observation is often the weakest link to biomarker development. This is in part because those who made the initial observation lack the tools (adequate finances, adequate infrastructure, adequate number of subjects, etc.) to validate the findings. Validation requires high throughput and access to large cohorts of well-defined clinical samples. A variety of candidate biomarkers (e.g., peptides, proteins, carbohydrates, DNA, RNA, metabolites) analyzed simultaneously optimizes yield and provides a direct comparison of the performance characteristics of each biomarker.

Choosing the proper type of sample for biomarker validation

Samples in the blood (serum, plasma): Serum and plasma are routinely used in clinical chemistry. Sample collection is minimally invasive and in some settings blood is the most practical sample to collect. Even though a marker may be diluted markedly in serum or plasma, much larger volumes can be obtained (1-5 mL) than are commonly collected in a breast specific body fluid such as NAF. In other words, a marker detected in NAF could be diluted by a factor of 1.000 or more and still be detected in routinely collected volumes of serum (39).

Breast specific samples: Both DL and NAF are collected from the breast ducts. The ductal epithelium gives rise the the vast majority of breast cancers. Unlike blood, the samples are not diluted by biomarkers contributed by other organs in the body. DL is more cellular than NAF, and therefore better for the analysis of intracellular components such as DNA and RNA, whereas NAF has a highly concentrated protein and carbohydrate content, and therefore is well suited for the analysis of the latter two types of biomarkers (39).

Conclusion

Great strides in breast cancer biomarker development have already been made to tailor treatment to individuals with newly diagnosed breast cancer. This is because the available tumor can be phenotyped through assessment of specific gene alterations, gene panels, or whole genome sequencing, to guide hormonal therapy, biologic therapy as well as chemotherapy. Tissue assessment is generally not as practical to screen healthy individuals, or to follow individuals long term after cancer treatment to monitor for disease recurrence. For early detection, body fluids are appropriate for biomarker development. Interventions on the breast with excisional biopsy followed by radiation or mastectomy make breast specific body fluid samples primarily useful for early detection, whereas serum/plasma is the logical body fluid for serial assessment of disease response and recurrence.

Biomarker panels are coming into increasing use. This multianalyte assessment is both practical and a reasonable approach to optimize sensitivity and specificity. Validation of biomarkers is critical before general clinical use.

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Review

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Gene Expression Profiling in Breast Cancer and Its Effect on Therapy Selection in Early-Stage Breast Cancer

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ABSTRACT

Breast cancer is a heterogeneous disease. The purpose of adjuvant therapy for early-stage breast cancer is to provide maximum benefit with minimum side effects and not to under-treat or over-treat. The clinical progresses of patients with the same clinical and pathological characteristics who are given similar treatments may show major differences. This fact indicates that the prognostic and predictive factors that we have used until recent years for therapy selection are not really sufficient, we need new markers, every disease and every individual are unique and that treatment should be individualized. The gene expression profiling, which has come into clinical use in recent years, is beneficial in therapy selection for luminal breast cancer cases. A differentiation can be made among patients for whom only endocrine treatment would be adequate and those who should also receive chemotherapy in addition to endocrine treatment. Several new gene expression analysis studies targeted at gaining the ability to determine drug selection in chemotherapy, endocrine treatment and neo-adjuvant therapy are also currently ongoing. The staging system for new breast cancer that is to be published in the year 2018 also includes gene expression analyses within the prognostic panel and the stage changes depending on the result. The statement 'Treat the patient, not the disease.' is becoming increasingly entrenched in our clinical practice. This article briefly summarizes the gene expression profiles, which are validated and used in the selection of therapy for early-stage breast cancer.

Keywords: Early breast cancer, molecular subtypes, gene-expression profiling, prognosis, staging

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Introduction

Breast cancer is the type of cancer with the highest incidence rate among women globally and it ranks the first among reasons for death due to cancer in women (1). Appropriate selection and administration of therapies according to the patient are important for not only prolonging disease-free survival and overall survival, but also for preventing late complications (such as anthracycline-related cardiac problems, myelodysplastic syndrome, leukemia and taxane-associated neuropathy) (2).

It is a standard approach to administer adjuvant chemotherapy (CT) and/or hormonal treatment (HT) to reduce the risk for metastasis according to the histological, pathological and immunohistochemical staining characteristics of the tumor following surgical treatment of early-stage breast cancer (3-5). The strongest predictors in determining the risk for metastasis are as follows: tumor diameter, histological grade, axillary lymph nodes (ALN) metastasis and hormone receptors (HR) and HER2 status as well as Ki-67 proliferation index (6). In recent years, molecular sub-types (intrinsic sub-types) of breast cancer have been described and therapy selection is done according to these sub-types (7-10). Breast cancers are divided into four sub-groups as per their molecular characteristics (11, 12): Luminal, HER2-positive, basal and normal-like (Table 1). CT is necessary for adjuvant treatment of basal-type and HER2-positive breast cancer cases.

Luminal tumors are HR-positive breast cancers that constitute approximately 60-80% of all breast cancer cases (8, 11, 12). Luminal tumors are divided into two groups as A and B: Their characteristics are summarized in Table 2. While luminal A tumors are very sensitive to HT, it may be necessary to use CT and HT together in luminal B tumors. The above-specified classical predictors are not

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Table 1. Breast cancer molecular subtypes (Modified from 11)

Intrinsic subtype	IHC* status	Grade	Prognosis	Prevalence
Luminal A	ER+/PR+;HER2-;Ki67 low	1/2	Good	40%
Luminal B	ER+/PR+;HER2-;Ki67 high ER+/PR+;HER2+;Ki67 any	2/3 2/3	Intermediate Intermediate	20%
HER2 overexpression	ER-/PR-;HER2+;Ki67 any	2/3	Poor	12 to 21%
Basal	ER-/PR-;HER2-;basal marker+	3	Poor	11 to 23%
Normal-like	ER+/PR+;HER2-Ki67 any	1/2/3	İntermediate	3 to 10%

*IHC: Immuno-Histo-Chemical Staining; ER: Estrogen Receptor; PR: Progesteron Receptor

Table 2: Characteristics of Luminal Subtypes Breast Cancers (Modified from 8)

	Luminal A	Luminal B
Incidence %	40	20
ER-related genes	High	Relatively low
HER2-related genes	Low	Variable
TP53 mutation	12%	29%
Proliferation-related genes	Low	High
Prognostic significance	Good	Poor
Prediction to endocrine therapy	Highly sensitive	Relatively less sensitive
Prediction to cytotoxic therapy	Less sensitive	Less sensitive

ER: estrogen receptor

sufficient to distinguish between the luminal A and B sub-groups in HR-positive, HER2-negative breast cancer and does not account for different clinical progresses of luminal type breast cancer patients who are in the same stage and receive similar treatments. In order to explain this difference and better differentiate between patients who may not require chemotherapy as part of adjuvant therapy and those who need to have addition of CT to their hormone therapy, various gene expression analyses have been and are being studied retrospectively and prospectively.

Gene Expression Profiling

Amsterdam 70-gene Profile- MammaPrint dx Test (Table 3)

The first one of these tests is MammaPrint dx 70-gene expression analysis, which was developed by the Netherlands Cancer Institute. They identified 70 genes which differentiate between patients diagnosed with breast cancer as good profile and poor profile depending on the risk of developing metastasis within 5 years as of diagnosis. This gene profile was developed based on a gene study conducted with 78 ALN-negative patients below the age of 55 and diagnosed with invasive breast cancer a tumor size <5 cm (13, 14). The test is conducted using the micro-array-based gene expression profiling technique. Fresh tissue sample or frozen archival material and formalin-fixed paraffin-embedded (FFPE) material are used for the test (9, 15). Several studies have demonstrated that MammaPrint is an independent prognostic factor in patients with ALN-negative breast cancer (16-18). It has been seen that 35% of patients that seemed to have high risk disease actually had low risk and 14% of patients that seemed to be in the low risk group actually had high risk in this program as compared to the adjuvant online program (19).

The MammaPrint test is recommended for early breast cancer of all ages with tumor size <5 cm, with the ALN 0-3 positive cases, and estrogen receptor (ER)-positive or negative tumors (8). It was approved by Food and Drug Administration (FDA) in 2007 for marketing as a prognostic test, but not to select therapy or predict response to therapy (15). Results are reported as low risk (13% chance of developing distant metastases at 10 years without adjuvant treatment) or high risk (56% chance of developing distant metastases at 10 years without adjuvant treatment).

For the prospective validation of the test, an international, randomized, Phase-3 MINDACT study (Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy-EORTC 10041/BIG 3-04 study) has been scheduled (20). In this study, 6693 patients with early-stage breast cancer (HR+, Nod 1-3 positive or negative, HER2-) were recruited. The genomic risks (using the 70-gene signature) and clinical-pathological risks (using a modified version of Adjuvant Online) of the patients were identified and the aim has been set as comparing their effectiveness in the adjuvant therapy selection. CT was not provided for the group with low genomic and clinical risk. CT was provided for the group with high genomic and clinical-pathological risk. In patients with discordant risk results, either the genomic risk or the clinical-pathological risk was used to determine the use of chemotherapy and hormone therapy or only hormone therapy. The primary aim of the study was to determine whether patients with high clinical risk and low genomic risk had requirement for CT. According to the assessment of 1550 patients with high clinical risk and low genomic risk, metastasis-free survival rate was found to be 94.7% in patients not receiving CT, which was 1.5% lower than the patients that were on CT. The rates of distant metastasis-free survival were found to be similar among patients that were node-negative or positive, ER-positive and HER2-. Based on these results, the researchers concluded that 46% of the patients with low genomic risk and high clinical risk did not require CT.

MammaPrint is featured as a prognostic parameter in the St Gallen and ESMO (European Society of Medical Oncology) guidelines (3, 21).

In the 8th Breast Cancer Staging System of American Joint Committee on Cancer (AJCC), which is to be published in 2018, gene expression profiling is included in breast cancer staging as a prognostic panel (22).

Table 3: Gene Expression Tests for Predicting Clinical Outcomes in Patients with HR positive, HER2 negative, Node 0-3 Positive Early Stage Breast Cancer (7, 9, 22, 34, 40)

	Oncotype DX	MammaPrint	PAM50-risk of recurrence score	Breast Cancer Index	EndoPredict
Manufacturer	Genomic Health (Redwood City, CA)	Agendia (Irvine, CA)	NanoString Technologies (Seattle, WA)	bioTheranostics	Myriad/ Sividon Diagnostics
Tissue Sample	FFPE	Fresh, frozen, or FFPE	FFPE	FFPE	FFPE
No of genes	16 cancer 5 control	70	50 cancer 22 control/ housekeeping + tumor size	MGI-5 cell cycle genes; H/I-Gene expression ratio	8 cancer 3 control
Technology	Quantitative RT-PCR	Microarrays	Quantitative RT-PCR	Quantitative RT-PCR	Quantitative-RT-PCR
Predictive	+	-	-	+	-
Prognostic	+	+	+	+	+
Eligible patients	ER+ and HER2-, T1/2 0-3 nodes f	Stage I-and II breast cancer	ER+, stage I/II 0-3 nodes	ER+ HER2- Node-	ER+ HER2-
Measure/ Categories	RS Low <18 Intermediate 18-31 High >31	Good risk and poor risk intrinsic subtype	ROR:Ten year probability of distant recurrence Low <10% Intermediate 10-20% High >20% Intrinsic subtype	Low, intermediate and high risk	The test result is composed of the 'molecular fingerprint' of a tumor in combination with the established prognostic parameters nodal status and tumor size
Strength of ASCO recommendation	Strong for N0 Moderate for N+	Moderate for N0 and N+	Strong for N0 Moderate for N+	Moderate for N0 Strong for N+ (don't use for N+)	Moderate for N0 and N+
8th AJCC breast cancer staging manual (when available as stage modifiers).	For patients with HR-positive, HER2 negative, and ALN negative tumors, Oncotype Dx recurrence score less than 11, regardless of T size, places the tumor in the same prognostic category as T1a-T1b N0M0, and the tumor is staged using the AJCC prognostic stage group table as stage I (Level of Evidence I).	For patients with HR-positive, HER2 negative, and ALN negative tumors, a MammaPrint low-risk score, regardless of T size, places the tumor in the same prognostic category as T1a-T1b N0M0 (Level of Evidence II).	For patients with HR-positive, HER2 negative, and ALN negative tumors, a PAM50 ROR score in the low-range, regardless of T size, places the tumor in the same prognostic category as T1a-T1b N0M0 (Level of Evidence II).	For patients with HR-positive, HER2 negative, and ALN negative tumors, a BCI in the low-range, regardless of T size, places the tumor in the same prognostic category as T1a-T1b N0M0 (Level of Evidence II).	For patients with HR-positive, HER2 negative, and ALN negative tumors, Endopredict low-risk score, regardless of T size, places the tumor in the same prognostic category as T1a-T1b N0M0 (Level of Evidence II).

AJCC: American Joint Committee on Cancer; ALN: axillary lymph node; ASCO: American Society of Clinical Oncology; FFPE: formaline-fixed parafine embedded; RT-PCR: reverse transcriptase-polymerase chain reaction; ER: estrogen receptor; HR: hormone receptor; BCI: Breast Cancer Index; ROR: Risk of Recurrence

One of these panels is MammaPrint (when available as stage modifiers): For patients with HR-positive, HER2 negative , and ALN negative tumors, a MammaPrint low-risk score, regardless of T size, places the tumor in the same prognostic category as T1a-T1b N0M0 (Level of Evidence II).

21-Gene Recurrence Score assay (Oncotype DX) (Table 3)

The Oncotype DX Breast Cancer Assay is a commercially available reverse transcriptase-polymerase chain reaction (RT-PCR) based signature. It evaluates the mRNA levels of 21 genes (16 cancer-related genes and 5 reference genes) (8, 9, 15). The expression of these 21 genes is reported as a single Recurrence Score (RS), which ranges between 0 and 100. The test is routinely performed on FFPE tissue specimens. Patients are divided into 3 risk groups depending on the risk for distant metastasis in ten years: 1- Low risk (RS<18) 2- Intermediate risk (RS 18-30) 3- High risk (RS>30)

The clinical validation of Oncotype DX was originally completed in 2 retrospective studies (National Surgical Adjuvant Breast and Bowel Project-NSABP B-14 and B-20 studies) (23, 24): In the NSABP B-14 study, patients (HR-positive disease with negative axillary nodes) were randomized to the tamoxifen versus placebo arms for 5 years (23). The distant metastasis-free survival rates of the patients as per their risk groups were as follows: Low risk group (RS<18; 10-year risk for distant metastasis: 6.8%); intermediate risk group (RS:18-30; 10-year risk for distant metastasis: 14.3%) and high risk group (RS>30; 10-year risk for distant metastasis: 30.5). In conclusion, Oncotype DX was inter-

preted as being a 'predictor of distant relapse in ER+ node negative disease.' These results were also tested in the NSABP B-20 study (HR positive disease with negative axillary nodes; adjuvant tamoxifen versus CMF + tamoxifen) and the contribution of CT as per the risk groups was investigated (24): It was seen that the addition of CT to tamoxifen for patients in the low risk group decreased the 10-year risk for distant metastasis by only 1.1% while the addition of CT to tamoxifen for patients in the high risk group reduced the 10-year risk for distant metastasis significantly by 27.6%. The benefit of the addition of CT to hormonal therapy in the intermediate risk group was not showed to be clinically significant.

The action to be taken for patients in the intermediate risk group could not be completely elucidated. Should it be only HT or CT and HT? In order to shed light onto this question, a prospective randomized study was initiated in the year 2006 (Trial Assigning Individualized Options for Treatment-TAILORx; prospective clinical validation study) (25). In this study, 10.253 patients (HR-positive and HER2-negative with negative axillary nodes) from 6 countries and 900 study sites were included between the years 2006 and 2010. The patients were divided into groups as follows: RS<11 low risk group (only endocrine treatment), RS 11-25 intermediate risk group (divided into two arms: only HT and CT + HT) and RS>25 high risk group (CT and HT). As part of HT, tamoxifen or aromatase inhibitor (AI) or tamoxifen followed by AI were administered for 5 years and tamoxifen or AI along with ovarian suppression were used in 3% of the patients. During the ESMO 2015 meeting, the results of the low-risk group (15.9% of all patients;-1626 patients) were presented as follows: 5-year invasive disease free survival: 93.8%; recurrence-free survival: 98.7%; distant recurrence-free survival: 99.3% and overall survival: 98%. Recurrence events were uncommon regardless of the histologic grade, tumor size and were not significantly affected by younger age at diagnosis in this low risk group.

The results of the study also prospectively showed that only adjuvant HT was sufficient for patients with low risk according to the 21 gene expression analysis (Level IA evidence). It is expected that the results of the intermediate risk group will be announced within the year 2017.

The prognostic and predictive validity of Oncotype DX was also retrospectively evaluated in 4 randomized phase-3 studies [SWOG 8814, ATAC (Adjuvant Tamoxifen or Anastrozole), NSABP-B28 and ECOG 2197 studies] including ALN positive and HR-positive cases (26-30). It was seen that CT was beneficial in distinguishing node-positive patients who would benefit from CT (Predictor of likelihood of chemotherapy benefit in ER+ Node positive disease). Its prospective validation in the node-positive patients was demonstrated in the West German Study Group Plan B Randomized Phase-3 study, the Clalit Registry study conducted in Israel and the SEER real-life observational study (31-33). In all these studies, the 5-year survival rate of patients in the low risk group is >95%.

Other ongoing trials (RxPONDER and OPTIMA) are evaluating whether adjuvant CT is beneficial in patients with HR-positive, HER2-negative breast cancer with 1 to 3 positive ALNs and a RS of 25 or less (7, 8).

Oncotype DX is included as a prognostic and predictive tests in the ESMO, St Gallen, NCCN (National Comprehensive Cancer Network; includes 1 to 3 positive nodes) and ASCO (American Society of Clinical Oncology; node negative only) guidelines (3, 4, 21, 34).

The Oncotype DX staging system has been included in the 8th breast staging system by AJCC (when available as stage modifiers) (22): For patients with HR-positive, HER2-negative and ALN-negative tumors, Oncotype DX recurrence score less than 11, regardless of T size, places the tumor in the same prognostic category as T1a-T1b N0M0, and the tumor is staged using the AJCC prognostic stage group table as stage I (Level of Evidence I).

Predictor analysis of microarray 50 risk of recurrence score (PAM50-ROR) (Table 3)

The PAM50 is a test that uses 50 classifier genes and 5 control genes. The microarray technique is employed and study is done on FFPE tissues with quantitative RT-PCR technology (8, 9, 15). Along with the tumor diameter and four main intrinsic sub-types are provided along with the risk of recurrence (ROR). The PAM50 score is reported on a 0-100 scale (ROR score of risk of recurrence), which is correlated with the probability of distant recurrence at ten years for women with HR positive, early-stage node-negative or node 1-3 positive breast cancer. Patients are divided into high (>20%), intermediate (10 to 20%) and low (<10%) risk groups. It was retrospectively tested in the ATAC and ABCSG-8(Austrian Breast Cancer Study Group 8) studies and demonstrated to be an important prognostic indicator for both ALN-negative and ALN-positive patients in all sub-groups (35, 36). It is an FDA-approved test (9, 34).

It has been included in the 8th breast cancer staging system by the AJCC (when available as stage modifiers) (22): For patients with HR-positive, HER2-negative and ALN-negative tumors, a PAM50 ROR score in the low-range, regardless of T size, places the tumor in the same prognostic category as T1a-T1b N0M0 (Level of Evidence II).

Breast Cancer Index (BCI) (Table 3)

Breast Cancer Index is a combination of molecular grade index (MGI) and HOXB13-to-IL17BR expression ratio (H:I ratio). Studies conducted have shown that it is effective in anticipating treatment response and prognosis in ER-positive tumors (37, 38). Three risk groups are identified: low, intermediate and high risk. Its clinical usability is still being investigated. ASCO states that it can be used in making a decision for adjuvant therapy in HR-positive, HER2-negative and node-negative disease while it is not recommended to be used in node-positive disease (34).

EndoPredict (Table 3)

It involves RNA-based analysis of 11 genes (8 cancer related and 3 reference genes). Its prognostic value was validated using the data from ABCSG-6 and ABCSG-8 trials (39). ASCO states that it can be used in making a decision for adjuvant therapy in HR-positive, HER2-negative and node-negative disease while it is not recommended to be used in node-positive disease (34). It is a test which can also be used to make a decision for prolonged adjuvant therapy.

Breast Cancer Index and EndoPredict (when available as stage modifiers) tests are also included as part of the prognostic panel in the 8th staging booklet (Level of evidence II) (22) (Table 3).

Other assays include the Rotterdam 76-gene signature, genomic grade index, molecular grade index, etc. There are not sufficient data about the prognostic significance of these arrays (9, 15, 34, 40, 41). Further studies are needed.

Conclusion

Gene expression analyses are beneficial in determining the prognosis and selecting therapy for luminal type breast cancers (HER2-negative, HR-positive). Even though these tests are costly, studies performed have shown that they are actually cost-efficient (42, 43). They are included in reimbursement schemes in the USA and Europe whereas they are not included in the reimbursement program in Turkey and many other countries. Therefore, studies can be conducted only on a limited group of patients. Studies conducted in Turkey have demonstrated that Oncotype DX has significantly correlated with PR and Ki-67 score of the tumor, and has a significant contribution to determining the therapy selection (44, 45). In another study from Turkey, Oncotype DX test was found as cost-effective in patients with early stage breast cancer (46).

It should also be kept in mind that gene expression analyses may yield false results in rarely seen tumors such as breast cancers showing neuroendocrine differentiation and in mixed morphologies (47). Furthermore, the stromal cells and inflammatory cells around the tumor tissue and the normal breast tissue are not included in the analysis. The ratio of non-neoplastic cells in the analysis may change the expression profile and the prognostic signature. In the second-generation gene expression analyses, myoepithelial and stromal cells are also assessed in addition to the epithelial cancer cells (8).

There are no gene expression tests available yet to determine the therapy selection for other intrinsic types of breast cancers. Various gene expression analyses and second generation gene expression analysis studies are ongoing with the aims of determining the drug selection in endocrine treatment, selecting the agent to be used in chemotherapy and predicting treatment to neoadjuvant therapy (8). Technological advancements and developments in the field of molecular biology and genetics will enable us to provide individualized therapies for our patients.

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Original Article

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The Effects of Training on Knowledge and Beliefs About Breast Cancer and Early Diagnosis Methods Among Women

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ABSTRACT

Objective: Breast cancer (BC) is the most common female malignancy in the world and Turkey. Its prevalence and mortality are surprisingly increasing at a rapid rate. The objective of this study was to determine the effectiveness of training sessions on women's knowledge of relevant risk factors of BC and screening methods, screening behaviors and health beliefs among of healthy women in Turkey.

Materials and Methods: In this study, in order to establish the efficiency of BC training, a semi-empirical single group pre-test & post-test research model was used. The data were collected by using a self-administered questionnaire and by using the Turkish version of Champion's health belief model scale (CHBMS). The pre-test was performed before the training and after one week of the training, post-test was performed with a questionnaire having the same content.

Results: In total, 244 women participated in the study. The average age of the women was 39.44 (SD=1.06) years. The mean total knowledge score increased significantly (p<.001) from 9.05 in the pre-test to 16.53 in the post-test. The results showed that both mean knowledge scores and CHBMS subscales scores of the women were increased significantly (p<.001) from the pre-test to the post-test. In multiple linear regression analysis, BC screening knowledge of women with susceptibility, benefit, self-efficacy and health motivation subscales of CHBMS, breast self-examination (BSE) practice and self-efficacy were also significant in the post-test; in the pre- and post-tests, a significant relationship among the level of education of women, susceptibility and seriousness was found (p<.001).

Conclusion: The study showed that the training program had profound effects on BC knowledge, screening behaviors and health beliefs of women.

Keywords: Breast cancer, health belief model, early diagnosis methods, breast cancer risk factors, training

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Introduction

International studies have indicated that breast cancer (BC) is one of the most fatal cancers that affect women and it is also a global health problem in both Turkey and the world. In 2012, the International Agency for Research on Cancer (IARC) stated that 1.7 million women were diagnosed with BC. Now, it represents one fourth of all cancers in women (1). In Turkey, according to the Ministry of Health's cancer statistics data, while BC in women was 35.0% in 2005, it rose to 45.9% in 2013 (2). These figures suggest that measures taken on an international dimension for the prevention of BC are very important not only in Turkey, but throughout the world. The reduction in BC mortality depends to a large extent on early diagnosis initiatives because BC pathogenesis is multifactorial, primary prevention is difficult. Therefore, it is important to identify it early. The World Health Organization (WHO) (2012) states that there are two components of early detection efforts: 1) Early diagnosis; the awareness of early signs and symptoms in order to get them diagnosed and treated at early stage. In the absence of any early detection or screening and treatment intervention, patients are diagnosed at very late stages when curative treatment is no longer an option. 2) Screening aims to identify individuals with suggestive abnormalities of a specific cancer or pre-cancer and refer them promptly for treatment or when feasible for diagnosis and treatment (3). Screening programmes are especially effective for frequent cancer types for which cost-effective, affordable, acceptable and accessible screening tests are available for the majority of the population at risk. The focus of BC screening is to reduce the disease mortality (4). In Turkey, a nationwide organization called Cancer

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Early Detection and Education Center (Kanser Erken Teşhis, Tarama ve Eğitim Merkezi-KETEM) has recently been launched by the Ministry of Health and began to screen for some cancers (2). It is recommended for early detection of BC, there are basically three methods of screening programs complementing each other; breast self-examination (BSE), clinical breast examination (CBE) and mammography (MMG) (5). This is emphasized in order to increase the effectiveness of the screening methods, it is needed to use two or three of the methods in combination. However, in this regard, studies published in many countries and in Turkey have shown that the rate of participation of women in the BC screening program was low (6-13). The reasons why women did not participate in the screening program included lack of information and pain ranking the first, not wanting to be exposed to radiation, being afraid to discover the cancer, embarrassment, fatalism, and misinformation, not seeing a physician unless ill, possibility that screening might be refused by the family, negligence, lack of physician recommendation, health-care provider attitudes, not remembering to do it, discomfort, and having not enough time to handle it (12, 14-19). The results of the studies indicate that knowledge, attitudes, and motivation are important individual determinants of health behavior. Also, many social, cultural, and economic factors contribute to the development, maintenance, and change of health behavior patterns (20). The health belief model (HBM) theorizes that people's beliefs about whether they are at risk for a disease or health problem, and their perceptions of the benefits of taking action to avoid it influence their readiness to take action (21). In Turkey and in many studies in various societies, training has been shown to increase the participation in screening programs and the BC information of women. In Turkey, the Ministry of Health, Department of Cancer established one of the primary objectives of public training to be the national screening program in 2004 (2, 22-27). The aim of this study was to determine the effects of the training given about BC, risk factors, health beliefs with knowledge and practices related to screening behavior to females who were trainees at an adult education center during the cancer week (April 1-5) in the Central Anatolia region of Turkey.

Materials and Methods

In this study, a semi-empirical, single group pre-test-post-test research model was used in order to establish the efficiency of BC training.

Participants and setting

The research was done with 244 volunteers in total aged 20 and over, who were women that were not diagnosed with BC. The study was conducted at a community education center located in Sivas, a city in the Central Anatolia of Turkey.

Instruments

In this study, the data were collected by using a structured questionnaire prepared by the authors themselves and the Turkish version of Champion's Health Belief Model Scales (CHBMS).

Questionnaire form

A questionnaire form was developed for this study by the researchers. The questionnaire form included two sections: the first section included demographic characteristics (e.g. age, education level, current marital status, work status) and BC risk factors of women (e.g. menarche age, family history of BC, personal history of BC, having any children, childbearing age, number of children, physique (thin, normal, obese), the use of oral contraceptives, menopausal status the use of postmenopausal hormone) and the screening practices. The second section included multiple-choice questions and it had 18 items, which measured the level of knowledge about BC risk factors and screening; 12 questions were about high risk factors for BC including age (>40), early menarche (<12 years), being a female who did not give birth, later age at first full-term pregnancy (>30 years), breast-feeding, long-term use of oral contraceptives, late menopause (>55 years), having first-degree relatives with history of breast cancer, physical exercise, smoking, high level of education and obesity and 6 questions were related to knowledge of BC screening (e.g. a woman was asked about BSE, CBE and MMG screening), each item was answered as true or false. The correct answers were scored as 1, wrong answers as 0. The higher scores indicated a higher level of knowledge about BC risk factors and screening. This form was applied before and after the training.

The health belief model scale

The Health Belief Model (HBM) was originally developed in the 1950s by social psychologists in the public health arena as a way of predicting who would utilize screening tests and/or vaccinations (28). The HBM Scale was developed in 1984 and was revised in later works by Champion (29, 30). Champion's revised tool has 42 items representing 6 subscales. The six basic concepts contained in the HBM are: susceptibility, seriousness, general health motivation, benefits, barriers, and self-efficacy as they relate to BC and BSE MMG self-efficacy (revised 1997), and it also included 7 items related to health motivation (revised 1993). All the items from the subscales were formatted using a five-point Likert scale. Each individual had six separate scores. In this study, the version of CHBMS was used that was adapted to Turkish by Karayurt and Dramalı (31). Cronbach's Alpha value for each subscale ranged from 0.58 to 0.89. For this study, Cronbach's Alpha value was determined as 0.74-0.88 in pre-test and 0.76-092 in post-test.

Training

The public education center serves in two different buildings. Therefore, training was conducted twice between the hours of 2:00 and 4:30 p.m. (April 1-5) in the afternoon on separate days. One week before, institutional managers announced that training about breast cancer would be provided to all women who were attending courses at the community health center. On the day of the training, the researchers went to the institution one hour before the training and completed the preparations for the hall. Later, women who wanted to participate in the training were gathered in the hall. Before the training began, the purpose of work was explained by the first researcher who gave the training and it was announced that volunteers would participate in the study, those who did not want to participate in the study could listen the training. Questionnaries for pre-test were distributed before the training started. Women completed the questionnaire in 15-20 minutes. The training program provided for women aimed to improve their knowledge about BC and to promote their practical performance of BC screening methods. The training program took place after the participants completed the pre-test. In the training, a power point presentation was given by the first author to women for improving their knowledge of BC and screening, which took 60-90 minutes. Specifically, a phase of the training program included the following: (a) high risk factors of BC (b) risk factors of BC; (c) symptoms of BC; (d) screening methods (BSE, and CBE, MMG) for the early detection of BC. The researchers went to the institution again one week later for the post-test. Women filled in their survey forms once again.

Data collection

The study was carried out in two phases: the first phase (pre-training phase) and the second phase (post-training phase).

First phase (Pre-training): The following tools and techniques were used: A pre-designed, structured interview questionnaire was used to collect the following data from the women: demographics and pre-test of knowledge scores, risk factors and screening methods for BC and scores for the CHBM.

Second phase (Post-training): The post-test was done by using the same pre-test questionnaire for evaluation of the impact of the training program. Women filled in their survey forms again after one week. Women's responses for the pre- and post-test questions were obtained via face-to-face interviews. The study continued for 4 weeks.

In this study, no ethics committee approval was obtained. Written permission was received from the institution where women worked. The purpose of the study was explained to the women during the first stage. Verbal consent was received from the women who voluntarily participated in the study.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences 22.0 (SPSS Inc.; Chicago, IL, USA). It was determined by the Shapiro-Wilk test that the data (-1.5 to +1.5) showed a normal distribution. Descriptive statistics were used to evaluate the socio-demographic characteristics of the sample. Early detection practices (BSE, CBE and MMG) and scores for the CHBM were analyzed with student t-test to compare the scores. The data were determined using frequency, mean and standard deviation Paired Samples-t test. For comparisons between pre- and post-test knowledge, the McNemar Chi-square test was used. Paired samples t-test was performed to determine the difference between repeated measurements. To determine the causal relationship between continuous variables, the multiple linear regression analysis was applied. The findings were evaluated at a 0.05 significance level with a 95% confidence interval.

Results

Participant characteristics

Table 1 describes the study population. The women had a mean age of 39.44 years (SD=1.06). Of the 244 women who participated in the study, most reported to be married (76.6%) and having elementary education (51.7%), being housewives (92.6%), doing no physical exercise (77.5%), having children, breast-feeding their children, having had a menarche age of 12-14 years (75.8%), not being in menopause (88.9%) and never having smoked (78.7%).

Knowledge score

Table 2 includes the states of the women who had the following knowledge levels: pre-test 53.7%, post-test 85.2% BSE; pre-test 50.8%, post-test 80.3% CBE; pre-test 74.2%, post-test 93.9% MMG for early diagnosis of BC and the difference between pre- and post-test was statistically significant. While the mean score for the questions about knowledge of BC risk factors at the pre-test was 3.65, it was increased to 9.36 in the post-test and the difference between pre- and post-test was statistically significant (-25.865, p=.000). While the mean knowledge scores for BC screening was 3.58 in the pre-test, it was increased to 6.65 in the post-test and difference between pre- and post-test was statistically significant (-22.916, p=.000). The total mean knowledge score increased significantly from 9.05 in the pre-test to 16.5 in the post-test and the percentage of correct answers increased at a statistically significant rate (-25.910, p=.000).

Table 1. Characteristics of the women

Characteristics	n (%)
Age (years)	
≤39 age	121 (49.6)
≥40 age	123 (50.4)
Mean age	X=39.44 (SD=1.06)
Marital status	
Currently married	187 (76.6)
Single, Divorced, Widowed	57 (23.4)
Education level	
Illiterate	31 (12.7)
Elementary	126 (51.7)
≥High school	87 (35.6)
Work status	
Employed	18 (7.4)
House wife	226 (92.6)
Physical exercise	
Yes	55 (22.5)
No	189 (77.5)
Body mass index	
<29 kg/m^2	159 (65.2)
>29 kg/m^2	85 (34.8)
Parity (n=204)	
Nullipara	50 (20.5)
1	24 (9.8)
≥2	168 (68.8)
Age at first birth (194)	
<30	178 (73.0)
≥30	10 (5.3)
Breast feeding (n=194)	
Ever	183 (94.3)
Never	11 (5.7)
Age at menarche	
↓11 age	14 (5.8)
12-14 age	185 (75.8)
↑15 age	45 (18.4)
Family history of cancer	
Yes	21 (8.6)
No	223 (91.4)
Contraceptive pill	
Ever	58 (23.8)
Never	186 (76.2)
Smoking	
Ever	52 (21.4)
Never	192 (78.7)
Menopause	
Yes	27 (11.1)
No	217 (88.9)

SD: standard deviation

Table 2. Distribution of pre- and post-test knowledge scores

	Pre-test (% correct)	Post-test (% correct)	Test	p
BC				
Knowledge	70.5	99.2	68.014	0.000
BC risk factors				
Knowledge	34.4	98.0	153.006	0.000
What risk factors of BC?*				
The probability of BC for women aged 40 and above	49.2	86.1	46.098	0.000
High levels of education	1.6*	58.2	137.007	0.000
Using oral contraceptives	23.4	77.0	129.008	0.000
Smoking	54.9	84.4	61.476	0.000
Family history	66.4	91.4	59.016	0.000
Females not breastfeeding her baby	56.1	91.0	81.103	0.000
Female who did not give birth	30.7	81.1	121.008	0.000
First pregnancy after the age of 30 years	16.8	76.6	140.167	0.000
Physical exercise	18.9	70.5	124.008	0.000
Early menarche	12.3	78.3	159.006	0.000
Late menopause	13.1	69.7	134.064	0.000
Obesity	21.3	72.1	122.008	0.000
Total mean risk factors knowledge score (12 item)	3.648±2.857	9.369±3.097	-25.910	0.000
Screening knowledge (What is needed for early diagnosis methods?)*				
BSE	53.7	85.2	73.114	0.000
CBE	50.8	80.3	68.122	0.000
MMG	44.3	75.4	74.013	0.000
BSE is required to protect against BC	73.4	95.5	50.161	0.000
Do you practice BSE every month?	59.7	66.5	18.776	0.000
MMG is required to protect against BC	75.4	90.2	29.167	0.000
BC screening knowledge score (6 item)	5.451±1.976	8.103±1.191	-22.751	0.000
Total mean knowledge score (18 item)	9.05 (SD=4.15)	16.53(SD=3.68)	-25.910	0.000

*answers are multiple; BC: breast cancer; BSE: breast self examination; CBE: clinical breast examimnation; MMG: mammography

Table 3. The difference between pre- and post-test CHBMS subscales and BC and screening knowledge of women

CHBMS subscales	Pre-test	Post-test		
	Mean±SD	Mean±SD	Test	p
Susceptibility	8.070±2.712	8.865±3.050	-5.362	0.000
Seriousness	21.008±6.680	21.853±6.863	-2.975	0.003
Benefits	15.012±4.376	16.184±4.229	-5.770	0.000
Barriers	27.316±7.130	26.160±8.028	3.037	0.003
Self-efficacy	30.098±8.468	36.586±9.216	-10.415	0.000
Health motivation	25.049±6.044	26.648±5.738	-5.872	0.000
Total	126.553±19.068	136.295±22.030	-9.143	0.000
BC screening knowledge score*	5.451±1.976	8.103±1.191	-22.751	0.000
BC risk knowledge score	3.648±2.857	9.369±3.097	-25.910	0.000

BC: breast cancer; CHBMS: champion's Health Belief Model Scale

Table 4. The results of linear regression analyses of an independent variable with CHBMS

CHBMS subscales	Independent variable	PRE-TEST							POST-TEST						
		B	SE	β	t	p	F	Model (p)	B	SE	β	t	p	F	Model (p)
Susceptibility	Stable	9.700	1.325		7.321	.000			6.222	1.698		3.664	.000		
	Age	-.017	.020	-.067	-.860	.391			.010	.022	.034	.432	.666		
	Education level	-.459	.133	-.247	-3.445	.001	3.342	.002	-.539	.143	-.257	-3.757	.000	5.511	.000
	Family history of BC	.303	.618	.031	.490	.625			.267	.678	.025	.394	.694		
	BSE practice	-.540	.387	-.093	-1.395	.164			-.586	.383	-.095	-1.530	.127		
	Having MMG	.867	.440	.147	1.972	.049			-.056	.465	-.009	-.121	.904		
	BC screening knowledge	.059	.107	.043	.556	.579			.529	.173	.206	3.048	.003		
	BC risk knowledge	-.053	.067	-.056	-.788	.431			.065	.065	.066	1.009	.314		
Seriousness															
	Stable	21.876	3.384		6.465	.000			21.215	4.039		5.253	.000		
	Age	-.036	.051	-.057	-.700	.485			-.017	.053	-.026	-.314	.753		
	Education level	-.072	.340	-.016	-.212	.832			-.723	.341	-.154	-2.121	.035		
	Family history of BC	1.538	1.579	-.065	.974	.331	.738	1.313	1.313	1.612	.054	.815	.416	1.391	.210
	BSE practice	.206	.988	.014	.208	.835			-1.129	.911	-.081	-1.240	.216		
	Having MMG	.808	1.123	.056	.720	.472			-.097	1.107	-.007	-.088	.930		
	BC screening knowledge	-.412	.272	-.122	-1.513	.132			.550	.412	.095	1.334	.183		
	BC risk knowledge	-.008	.171	-.003	-.045	.964			-.010	.153	-.004	-.063	.950		
Benefit															
	Stable	13.570	2.204		6.157	.000			8.836	2.423		3.647	.000		
	Age	-.019	.033	-.045	-.558	.577			.004	.032	.011	.139	.890		
	Education level	.138	.222	.046	.623	.534			.072	.205	.025	.350	.727		
	Family history of BC	-.744	1.029	.048	-.724	.470	1.132	.344	-1.360	.967	-.090	-1.407	.161	3.334	.002
	BSE practice	-.153	.644	-.016	-.238	.812			-.058	.546	-.007	-.105	.916		
	Having MMG	1.142	.731	.120	1.562	.120			1.049	.664	.116	1.579	.116		
	BC screening knowledge	.254	.177	.115	1.432	.154			.846	.247	.238	3.417	.001		
	BC risk knowledge	-.034	.112	-.022	-.307	.759			.029	.092	.021	.319	.750		
Barrier															
	Stable	35.124	3.562		9.860	.000			29.849	4.750		6.284	.000		
	Age	-.021	.054	-.031	-.391	.696			.015	.063	.020	.243	.808		
	Education level	-.612	.358	-.125	-1.708	.089			-.458	.401	-.083	-1.142	.255		
	Family history of BC	-1.178	1.662	-.046	-.709	.479	1.709	0.108	1.750	1.896	.061	.923	.357	1.009	.425
	BSE practice	-1.772	1.040	-.116	-1.704	.090			-1.171	1.071	-.072	-1.093	.275		
	Having MMG	.711	1.182	.046	.601	.548			.727	1.302	.042	.558	.577		
	BC screening knowledge	-.262	.287	-.073	-.913	.362			-.301	.485	-.045	-.621	.535		
	BC risk knowledge	-.010	.180	-.004	-.057	.955			-.128	.180	-.049	-.710	.478		
Self-Efficacy															
	Stable	19.284	3.817		5.053	.000			18.382	5.169		3.556	.000		
	Age	-.051	.058	-.064	-.890	.375			.089	.068	.102	1.300	.195		
	Education level	-.005	.384	-.001	-.013	.990			.044	.437	.007	.100	.920		
	Family history of BC	-.730	1.781	-.024	-.410	.682	9.810	.000	-3.895	2.063	-.119	-1.888	.060	4.931	.000
	BSE practice	3.997	1.115	.220	3.586	.000			-.448	1.166	-.024	-.384	.701		
	Having MMG	-.750	1.266	-.041	-.592	.554			.860	1.417	.044	.607	.544		
	BC screening knowledge	1.638	.307	.382	5.334	.000			2.105	.528	.272	3.986	.000		
	BC risk knowledge	-.286	.193	-.097	-1.480	.140			.141	.196	.047	.718	.473		
Health motivation															
	Stable	20.314	3.037		6.690	.000			15.991	3.305		4.838	.000		
	Age	.090	.046	.158	1.972	.050			.078	.044	.144	1.788	.075		
	Education level	.563	.305	.136	1.845	.066			.186	.279	.047	.665	.507		
	Family history of BC	.396	1.417	.018	.279	.780	1.305	.249	-1.235	1.319	-.060	-.936	.350	2.927	.006
	BSE practice	-1.067	.887	-.082	-1.203	.230			.086	.745	.007	.115	.909		
	Having MMG	-1.004	1.008	-.076	-.996	.320			-.475	.906	-.039	-.525	.600		
	BC screening knowledge	.352	.244	.115	1.439	.151			1.009	.338	.209	2.991	.003		
	BC risk knowledge	-.019	.154	-.009	-.126	.899			.060	.126	.032	.479	.632		

BC: breast cancer; CHBMS: Champion's Health Belief Model Scale; MMG: mammography; BSE: breast self-examination

Health beliefs

As shown in Table 3, the women's post-test CHBMS subscales scores (susceptibility perception (-5.362, p=.001); seriousness perception (-2.975, p=.003); benefits perception -5.770, p=.001); barrier perception (3.037, p=.003); self-efficacy perception (-10.415, p=.001); health motivation perception (-5.872, p=.001) were found to be statistically significant in all dimensions compared to pre-test.

Multiple linear regression results are given in Table 4. As seen in the table, the relationship between the CHBMS sensitivity subscale and the variables was statistically significant (p=.000) and education level of women (ß=-.539) and knowledge level of breast cancer screening increased the post-training sensitivity level (ß=-.529) while the other variables did not affect the sensitivity subscale (p>.05). There was no significant relationship between CHBMS severity subscale scores and variables (p=.210). In the post-test, the relationship between CHBMS benefit sub-dimension and women's variables was significant (F=3.334; p=.002). After training, the increased breast screening knowledge of women increased the average score of benefit subscale (ß=-.846) while the other variables did not affect the utility sub-dimension (p>.05). The correlation between pre- and post-test of CHBMS obstacle perception was not significant (p=.425), self-efficacy perception was significant (p=.000). After the training, increased breast self-esteem score of women (ß=2.105) increased the self-efficacy perception score and the relationship between health motivation and variables was significant (p=.006). Also, the increased post-training breast screening knowledge increased the level of perceived health motivation as it was determined (ß=1.009) (Table 4).

Discussion and Conclusion

The most crucial means to develop protective behavior against the disease in the community can be realized by providing training programs for increasing knowledge and creating awareness among people. These study results revealed that, while the knowledge of BC among women was at a low level in the pre-test, it was significantly increased in the post-test. The present study demonstrated that training intervention was effective on increasing women knowledge and beliefs about BC. The results of the present study agreed with the findings by Açıkgöz et al. (32) and Ceber and colleagues in Turkey (22). The results of this study were similar to studies conducted in western Kenya, in Jordan, in the New York State Capital Region, in Taiwan, in studies conducted with immigrant Latino women and in Egypt and they revealed that there was a highly significant improvement in all knowledge items delivered to the intervention group from the pre to the post-test (6, 27, 33-36). As can be understood from the results of the above previous studies, training is the best way to increase knowledge.

Experimental and clinical studies indicate that preventing BC is a critical priority in women' health. Screening programs have a significant impact on prognosis in BC because it is the key to change BC growth rates via early detection and screening to facilitate the treatment of BC. In the current study, women did not have sufficient knowledge and practice about screening activities related to BC before the training. After the training, scores in the BC, screening knowledge and CHBSM subscale scores were increased. BSE is a way that enables a woman to check her breast for changes such as lumps or thickenings. It is still considered a simple, noninvasive, inexpensive, affordable and accessible method for younger and high-risk women to discover early changes in their breasts. Awareness and education on breast health issues have been identified as a key component of early detection (37). Hence, training programs can increase the BC awareness and ensure the regular performance of BSE and MMG. In one study, barriers against implementation of BC screening methods in women were found to be related to the level of education and lack of adequate information about BC screening (38). Recent pre- and post-test research in Turkey (32) determined that the average knowledge level of women was significantly increased after completion of the planned training as compared to the pre-training level. Similarly, Avci and Gözüm (39) found that education was effective in changing health beliefs regarding BC screening. In the study conducted by Abd El-Hay, it was emphasized that MMG could reduce mortality rates for women aged 40 to 74 by 25%. However, previous studies (7, 40-43) reported that the rate of practicing MMG among women was low. MMG has been the "gold standard" thanks to the detection of BC at an early stage for decades. Previous studies showed that educational interventions had a significant impact on increasing the frequency of having MMG and positive attitudes toward MMG (44), BC knowledge and BC health beliefs (45).

In the current study, women' health beliefs post-test scores after the training were increased significantly in all dimensions compared to the pre-test scores.

Women's education level and BC screening knowledge score and BSE practice were significantly associated with perceived susceptibility, perceived benefit, perceived self-efficacy and health motivation subscales of the CHBMS. No significant associations were found with the barrier subscale. Previous studies have shown that knowledge is also an important element in the health beliefs and health beliefs have a significant impact on acquiring positive health behaviors (22, 39). Therefore, accurate information clears the way for the development of health beliefs and has been associated with an increased rate of using the screening methods (6, 28, 36, 40, 45).

In this study, we identified that women had increased knowledge about BC, BC risk factors, and screening after the training. Group training appeared effective for improving BC knowledge, behaviors and health beliefs among women. The information gathered in this study is useful for planning educational programmes.

Limitations of the study

The study has several limitations. In the study, the level of knowledge of women after education evaluated after one week and it was not determined whether education had triggered behavioral change. It may be recommended that studies be carried out using a combination of methods at longer intervals for evaluating the effectiveness of the training. This limitation needs to be considered when interpreting the results of this study.

The results of this study suggest that women's beliefs and practices and knowledge were significantly increased in the post-test. However, training should be continued because increased knowledge level is important to change behavior about early diagnosis for BC and beliefs.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

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Original Article

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An Adaptation of the Short-Form Supportive Care Needs Survey Questionnaire (SCNS-SF 34) into Turkish

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ABSTRACT

Objective: In the study, Adaptation of The Short-Form Supportive Care Needs Survey Questionnaire (SCNS-SF 34) into Turkish, examination of its validity and reliability was aimed at.

Materials and Methods: The study was carried out between May and July, 2016 with 170 patients. The socio-demographic and clinical status was analyzed by means of number averages and standard deviation. After language validity, the content validity index was calculated. The split-scale analyses, which are reliability internal consistency tests, were performed with the Cronbach α coefficient and total item correlation. For structure validity, exploratory factor analysis was used.

Results: The average age of the patients is 55.53±11.43 years and average time since diagnosis is 5.69±5.06 years. The content validity index of the scale was calculated as 0.83. The Cronbach α coefficient is 0.93. In terms of the item total score correlation, all correlation coefficients except items 18 and 19 were between 0.36 and 0.81 and $p<0.001$. Items 18 and 19 were excluded. Following the exploratory factor analysis, items 13, 17 and 32 were excluded as their two detected high weight values were below 0.10. The descriptive factor analysis of item 29, four factors with eigenvalues over one and the total variance described by these four values was 68.83%. The factors were determined to be healthcare service and informing, psychology, sexuality and daily life.

Conclusion: It was confirmed that the SCNS-SF 29^{Tr} is a valid and reliable means for the Turkish society for the determination of the supportive care needs of breast cancer patients.

Keywords: Supportive care, breast cancer, validity, reliability

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Introduction

Determining and managing the unfulfilled supportive care needs of the patients is among the base components of healthcare (1). Supportive care may be considered as the determination of the care needs of the patients with and patient-centered approach and fulfilling those needs effectively (2). Before and during diagnosis, throughout the treatment, in the terminal period, it is the supportive care that helps the patient and the family to cope with the illness (3).

Breast cancer is the most common cancer type among Turkish women. Every one out of four women diagnosed with cancer has breast cancer. The number of the women diagnosed with breast cancer in one year is 17.531 in Turkey (4). It is vital to acknowledge the complete effects of the unfulfilled needs of breast cancer patient on their quality of life to take effective and timely action. Various studies have shown that the unfulfilled care needs of cancer patients occur mostly in the early stages of cancer survival and that this has a negative effect on life quality of patients (5-7).

Besides, various other studies put forward that supportive care is associated with longer survival and better life quality (7-9). In this respect, it is necessary to determine the supportive care needs of breast cancer patients and improve their quality of life. Patients have a multitude of care need dimensions; these dimensions include physical, practical-daily life activities, economic, environmental, cultural, knowledge, communication, emotional, psychosocial, psychosexual, spiritual-existential areas (10). Identifying unfulfilled needs will enable the improvement of the resources of cancer patients and the re-planning of the care (3). Recently, an interest in formal and systematical identification of care

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needs has been rising. The Cancer Patient Needs Questionnaire and the Supportive Care Needs Survey are commonly-used scales for this identification (10, 11). In Turkey, there is not a valid and reliable assessment instrument to identify the supportive care needs of cancer patients.

The Long-Form Supportive Care Needs Survey (SCNS-LF 59) and The Short-Form Supportive Care Needs Survey Questionnaire (SCNS-SF 34) have been designed so as to evaluate the care needs of cancer patients (12). SCNS-SF 34, has been translated to the original languages of China, Germany, France, Japan, Australia, Italy and Mexico, and has been proven to be a valid and reliable assessment instrument for identifying the care needs (13-20). The SCNS-SF 34 consists of 34 items aimed at identifying the needs of cancer patients and related with five areas which are psychology, healthcare system and information, physical and daily life and sexuality. A high score leads to the consideration that the perceived care need is high (12).

The validity of an assessment instrument amounts to its ability to assess the targeted feature truly and independently of any other feature whilst the reliability of an assessment tool is producing similar data viably under the same circumstances. It is recommended that the validity and reliability of the scales developed in other cultures, introduced in publications and their validity and reliability and other qualities well-identified be performed while adapting them to the Turkish society (21, 22). In identifying the validity and reliability of scales, language validity in psycholinguistic assessment, and validity and reliability tests in psychometric assessment is indispensable (22).

Based on these approaches, the aim was to tailor the SCNS-SF 34, which deals with the supportive care needs of cancer patients, to Turkish and investigate its validity and reliability.

Materials and Methods

Type of research

This is a methodological research done with the aim of testing the validity and reliability of SCNS-SF 34, designed to identify the supportive needs of breast cancer patients, in Turkey.

Population and sample of the study

The population of the study consisted of patients diagnosed with breast cancer who were admitted to the breast diseases polyclinic of a university hospital, between May and July, 2016. In the case of methodological researches, it is advised that the number of the samples be at least five times the number of the scale items (23). Due to the fact that SCNS-SF includes 34 items, 170 patients diagnosed with breast cancer - being at least five times the number of scale items - were included in the sample. Patients who were diagnosed at least one month before - since the questions of the items of SCNS-SF 34 assess the recent month - , willing to take part in the study, over 18 years of age and have no cognitive or/and oral or/and physical disorders were included.

Data collection tools

The research data was collected via the Socio-demographic and Clinical Status Form. The SCNS-SF 34 was used via being adapted to the Turkish social structure. The SCNS-SF 34 is made up of 34 items identifying the needs of cancer patients. It has a five-factor structure consisting of health system and information, psychological, physical and daily living, patient care and support, sexuality needs. The participants who are cancer patients were asked to identify their need for within the recent month help using the five answer choices. These five choices in the scale were measured with the following Likert-type items; 1=Not applicable, 2=Satisfied, 3=Low need, 4=Moderate need, and 5=High need. The sub-dimension scores are attained by the addition of each item points. A high score means leads to evaluate that the perceived need is high. Alternatively, the scale can be used to elicit information about the (non-)existence of the perceived unfulfilled needs and their numbers (a grade of 3 or higher stands for an unfulfilled need). The explained variance in the original study is 73% and the Cronbach α value is between 0.86 and 0.90 in sub-dimensions (12).

Ethics of the study

A written permit was obtained from the Ethical Committee of Ege University Nursing Faculty for the study (Decision dated 23.11.2016 and numbered 27344949/525-3132). Also, permission from Dr. Allison Boyes, the Head of the Center of Healthcare Researches and Psycho-Oncology of New South Wales Cancer Council, who created the SCNS-SF 34, to use the scale was received. A written permit was obtained from Ege University School of Medicine Hospital (Decision dated 18.01.2016 and dated 27344949-28-200). The patients were informed about the aim and the procedure, and their verbal consent was received prior to the study.

Translation of the scale to Turkish

Initially, the language adaptation of the SCNS-SF 34 was performed. The SCNS-SF 34 was first translated to Turkish from English by the researchers. Following this, it was translated to Turkish by two native speaker linguists separately for language validity. The translations were assessed by the researcher and a specialist faculty member, via taking the opinion of a Turkish language specialist and the most appropriate translation was chosen. Later, the form that had been translated into Turkish was back-translated to its original language by an expert who is well-familiarized with the original language of the scale and the culture of the language, and another expert who knows Turkish well. This translation was compared with the original and the Turkish versions of those items that did not match were revised. The translation was later assessed by nine nursing and one medical faculty members to finalize the scale. Its language validity having been established, the scale was applied on ten patients and it was revealed that the items were found as understandable by the patients.

Statistical analysis

The data obtained from the research was analyzed using the Statistical Package for the Social Sciences for Windows 21.0 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) package software. The socio-demographic and clinical statuses of the patients were analyzed with numbers, percentages, averages and standard deviation.

For validity test, expert opinions on content validity were taken and the content validity index (CVI) was figured. For the numeric verification of the content validity, the experts were provided with a grading scale developed by the researchers. The content validity test was performed with a technique developed by Davis (1992). The Davis technique grades expert opinions in a four-choice way. The choices are as follows; 1=not relevant, 2=somewhat relevant, 3=quite relevant, 4=highly relevant. The CVI is found out by dividing the number of the experts that mark the choices and with the total number of the experts and subtracting 1. Instead of comparing this value with a statistical scale, the 0.80 value is accepted as the criterion (3, 4, 24-26).

The reliability of SCNS-SF 34 was assessed with internal consistency tests. Internal consistency is the reliability test which identifies whether a scale has the ability of assessing with all its aspects (27). With this aim,

initially the split half method was used with Cronbach α coefficient and item-total score correlation in the internal consistency analysis of SCNS-SF 34. The scale items were divided into the first half and the second half. The Cronbach α coefficient was calculated. The Cronbach α reliability coefficient is a weighted standard variation average which is found by comparing the total variance of the items with the general variance. According to the numeric quantity of the Cronbach α reliability coefficient value, the reliability and the internal consistency of the scale is regarded as follows; α<0.40=not reliable, 0.40≤α<0.50=very low reliability, 0.50≤α<0.60=low reliability, 0.60≤α<0.70=sufficient reliability, 0.70≤α<0.90=high reliability, α≥0.90=very high reliability. Item total score correlation was also performed. That the correlation coefficient for each item of a scale is high shows that the item can effectively and sufficiently test the aimed behavior. It is recommended that the acceptable correlation coefficient be over 0.25 in item selection (28). Whether the scale catered for the target group and the homogeneity of the individuals in the group and the items were analyzed with the Hotelling's T^2 test. On condition that the individuals are not homogenous, the reliability of the scale might be low due to the difference of the target society even if the scale is a reliable one.

The exploratory factor analysis was used for structural validity. A principle component analysis was done. Since a correlation among the factors was found, oblique rotation was used for factor analysis. With the aim of assessing the compatibility of the date, the Bartlett's sphericity test and the Kaiser-Meyer-Olkin (KMO) test was performed. According to the KMO criteria, 0.90-1.00 is perfect, 0.80-0.89 is very good, 0.70-0.79 is good, 0.60-0.69 is mediocre, 0.50-0.59 is weak and below 0.50 is not acceptable (23). The fact that the KMO value is over 0.50 shows that the sample size is appropriate for validity analysis (27). If an item shows a high weight value in two factors, the difference is considered. The minimum difference between two high weight values should be 0.10. If the difference is smaller than 0.10, the item is a cyclical one and should be removed (29).

Results

Participant characteristics

The average age of patients was 55.53+11.43 years. The majority of patients were female (%97.1) and married (88.2%). 45.9% of patients graduated from primary school and 67.6% of patients were unemployed. 44.1 % of patients had Stage 1 breast cancer and the average time since the diagnosis was 5.69±5.06 years. An overview of the socio-demographical status of the patients that took part in the study is shown in Table 1.

Content validity of the scale

The SCNS-SF 34 was submitted to ten experts that consented to assess it. The assessing experts were nine faculty members of nursing and one specialist physician. Following the ascertainment of the experts, the CVI was calculated. The CVI of the SCNS-SF 34 items is 0.80-1.00. The CVI of the scale was found out to be 0.83.

Scale reliability analyses

The split half method that was used for the internal consistency analysis of SCNS-SF 34 included the division of the scale items as the first half (17 items) and the second half. The α value for the first half is 0.87 while it is 0.92 for the second half. The Spearman-Brown coefficient for the whole of the scale is 0.74. The Guttman Split-Half coefficient is 0.73. These results indicate that the scale is a reliable one with internal consistency. By the analysis (Hotelling's T^2 test=425.742, F=10.45, p<.001), it can be maintained that the scale is a powerful and authentic one that consists of homogenous structures. The Cronbach α reliability coefficient, calculated in the scope of internal reliability, was detected as 0.93. The item-score correlation that reveals how related the items were with the whole of the scale is given in Table 2.

Table 1. The characteristics of the patients (n=170)

	Mean±SD	Min.- Max.
Age (years)	55.53±11.43	19-79
Diagnosed time (years)	5.69±5.06	1-25
	n	**%**
Gender		
Female	165	97.1
Male	5	2.9
Marital status		
Married	150	88.2
Single	20	11.8
Education		
Primary school	78	45.9
Secondary school	36	21.2
High school	32	18.8
University	5	2.9
Postgraduate	19	11.2
Occupation		
Employed	16	9.4
Unemployed	115	67.6
Retired	39	22.9
Cancer stage		
Stage I	75	44.1
Stage II	72	42.4
Stage III	18	10.6
Stage IV	5	2.9
Type of treatment		
Surgery	34	20.0
Surgery+Chemotherapy	33	19.4
Surgery+Radiotherapy	18	10.6
Surgery+Hormone Therapy	3	1.8
Surgery+Chemotherapy+ Radiotherapy	57	33.5
Surgery+Chemotherapy+ Hormone Therapy	7	4.1
Surgery+Radiotherapy+ Hormone Therapy	4	2.4
Surgery+Chemotherapy+ Radiotherapy+Hormone Therapy	14	8.2
Total	170	100

SD: standard deviation; Min: minimum; Max: maximum

Table 2. The principal analysis results of the SCNS-SF34

Factor	Item number	Items	Factor loadings	Item total score correlation
Health care service and informing	27	Being informed about your test results as soon as feasible	0.87	0.77
	29	Being informed about things you can do to help yourself to get well	0.87	0.81
	28	Being informed about cancer which is under control or diminishing (i.e., remission)	0.87	0.74
	26	Being adequately informed about the benefits and side-effects of treatments before you choose to have them	0.85	0.76
	23	Being given written information about the important aspects of your care	0.81	0.76
	21	Hospital staff attending promptly to your physical needs	0.81	0.68
	22	Hospital staff acknowledging and showing sensitivity to your feelings and emotional needs	0.81	0.70
	24	Being given information (written, diagrams, drawings) about aspects of managing your illness and side-effects at home	0.80	0.76
	25	Being given explanations of those tests for which you would like explanations	0.79	0.78
	12	Learning to feel in control of your situation	0.78	0.62
	20	Reassurance by medical staff that the way you feel is normal	0.78	0.61
	33	Being treated in a hospital or clinic that is as physically pleasant as possible	0.70	0.67
	34	Having one member of hospital staff with whom you can talk to about all aspects of your condition treatment and follow-up	0.68	0.63
Internal consistency coefficients α: 0.95				Variance %36.16
Psychology	8	Feelings of sadness	0.78	0.60
	9	Fears about the cancer spreading	0.77	0.61
	7	Feeling down or depressed	0.77	0.56
	6	Anxiety	0.76	0.44
	10	Worry that the results of treatment are beyond your control	0.73	0.42
	11	Uncertainty about the future	0.71	0.43
	14	Feelings about death and dying	0.70	0.42
	30	Having Access to Professional counselling (e.g. psychologist, social worker, counsellor, nurse specialist) if you family or friends need it	0.50	0.43
Internal consistency coefficients α: 0.88				Variance %15.47
Sexuality	15	Changes in sexual feelings	0.90	0.42
	16	Changes in your sexual relationships	0.89	0.41
	31	Being given information about sexual relationships	0.80	0.43
Internal consistency coefficients α: 0.91				Variance %10.07
Daily life	2	Lack of energy/tiredness	0.91	0.44
	3	Feeling unwell a lot of the time	0.82	0.45
	4	Work around the home	0.73	0.41
	5	Not being able to do the things you used to do	0.66	0.55
	1	Pain	0.53	0.45
Internal consistency coefficients α:0.83				Variance %7.12
The Cronbach α coefficient=0.93				Total variance %68.83
Kaiser-Meyer-Olkin=0.84				Bartlett's Sphericity test x^2=4959.326 (p<.001)

SCNS: supportive care needs survey

Following the investigation of the item-total score correlations of the SCNS-SF 34, items 18 and 19 were removed as their correlation coefficient was below 0.25. The correlation coefficient of the other items were between 0.36 and 0.81, and the importance level of α=0.001 was statistically significant (p<0.001).

Structural validity of the scale

An exploratory factor analysis was done with the aim of assessing the structural validity of the SCNS-SF 34. The Bartlett's sphericity test gave the 5456.597 value and p<0.01 level, and the Kaiser-Meyer-Olkin (KMO) sample value was 0.84.

In line with these results, it was determined that 32 items were formed by identifying the total variance as 65.95% under four factors. The variance identified by the first factor was 35.41%; the variance identified by the second factor was 14.26%; the variance identified by the third factor was 9.50%; and the variance identified by the fourth factor was 6.77%. Following the examination of the factor weights of the 32-item scale, items 17 and 32, which were determined as cyclical items and had a difference of at least 0.10 between two weight values, were removed. Item 13 was also removed after the analysis following the removal of the above-mentioned items, as it weighed value on multiple items and the analyses were re-performed with the remaining 29 items. After the repetition of the analyses, it was found out that the 29 items identified in the ratio of 68.83 under four factors. The variance identified by factor one was 36.16%; the variance identified by factor two was 15.47%; the variance identified by the third factor was 10.07%; and the variance identified by factor four was 7.12%. The factor weights, the variance ratios that they identify, their internal consistency coefficients, their KMO values and the findings of the Bartlett's sphericity test are given in Table 2.

Discussion and Conclusion

The study was conducted in a methodological manner with the aim of adapting the SCNS-SF 34 to Turkish society and testing its validity and reliability. During the validity and reliability analyses, its internal consistency, language, content and structural validity were dealt with.

The adaptation of the SCNS-SF 34 to Turkish society was tested on breast cancer patients. It was found out that patient groups diagnosed with breast cancer, prostate cancer, colorectal cancer and other solid cancer types were worked with in the studies in various societies (13-20).

The CVI of the scale was 0.83. It was elicited that the experts had a consensus on the content of the items. Following the content validity analysis of the SCNS-SF 34 adapted in Mexico, a replacement or removal of the items was not exercised since the CVI was bigger than 0.7 in all the items (20).

In the internal consistency analysis of the SCNS-SF 34, the total item correlation of items 18 and 19 were detected below 0.25. That the correlation coefficient of each item is high shows that the item can effectively and adequately assess behavior. The acceptable correlation coefficient being over 0.25 is recommended (28). Therefore, these items were excluded from the scale. The correlation of the items related with indecisiveness is high. This is because a high number of specialist or hospital options exist. This can be interpreted as the patients' contentedness with the healthcare given in the hospitals and their oncologists.

The Bartlett's sphericity test that was conducted to assess the structural validity of the SCNS-SF 34 gave out a value of 5456.597and a level of p<0.01. This result indicates that the data set is appropriate for a factor analysis. KMO sample value was 0.84. The fact that the KMO criterion is 0.84 means that the sample size is quite convenient. As a result of the 32-item factor analysis, items 17 and 32 were removed from the scale due to having a detected high weight value difference that is over 0.10, and the test was repeated. After the re-test, item 13 was also removed since it was loaded more than once. The analyses were repeated with 29 items. It was seen that the total variance of 29 items under four factors was 68.83%. The Cronbach α value of four factors differs between 0.83 and 0.95. While the developed original structure of the scale is a five-factor one, the total declared variance is 73%. The Cronbach α value of the factors varies between 0.86 and 0.96 (12). The SCNS-SF 34 adapted to the Mexican society is a five-factor scale and the declared total variance is 59%. The Cronbach α value of the factors vary between 0.78 and 0.90 (20). The SCNS-SF 34 for the German society consists of five factors. Its total declared variance between 34 factors is 68%. The Cronbach α value between the factors varies between 0.82 and 0.95 (15). The SCNS-SF 34 adapted to the Chinese society has four factors and 33 items. The total declared variance for the items is 54%. Between the factors, the Cronbach α value varies between 0.75 and 0.92 (13) The SCNS-SF 34 for the Australian society is made up of five factors and the total declared variance for its 34 items remains unspecified. The Cronbach α value of the factors varies between 0.82 and 0.96 (18). Having five factors, the total declared variance of the 34 items of the SCNS-SF 34 adapted to the Japanese society is 74.6%. The Cronbach α value between the factors varies between 0.87 and 0.96 (17). Based on cultural differences, addition, removal or alteration of items can occur. In other words, in case of an item of the scale being not appropriate for the culture it is adapted to, the item can be altered or removed. In this study, the differences are the cultural differences in terms of perceiving the scale.

The Short-Form Supportive Care Needs Survey Questionnaire in Turkish (SCNS-SF 29^{Tr}) is a valid and reliable instrument for the Turkish society in terms of identifying the supportive care needs of breast cancer patients. The scale contains a total of 29 items. Its validity has been established via language validity, content validity and structure validity.

Using the SCNS-SF 29^{Tr} on breast cancer patients in the scope of prospective-identifying studies, with the aim of identifying their needs, testing it for the identification of other cancer patients' needs and working with larger patient groups are recommended.

Ethics Committee Approval: Ethics committee approval was received for this study from Ege University Nursing Faculty.

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Original Article

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Factors Influencing Non-sentinel Node Metastasis in Patients with Macrometastatic Sentinel Lymph Node Involvement and Validation of Three Commonly Used Nomograms

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ABSTRACT

Objective: Omitting axillary lymph node dissection (ALND) in a subgroup of patients with sentinel lymph node (SLN) metastasis is becoming a widely accepted practice. Avoiding the well-known complications of ALND is the sole aim without compromising the curative intention of surgery.

Materials and methods: The data were probed for breast cancer patients that were operated on between February 2014 and June 2016. SLN biopsies were performed in 507 patients and out of 157 patients who underwent ALND for a metastatic SLN, 151 were found eligible for the analyses as having macrometastatic (>2mm) SLN. MD Anderson, Memorial Sloan Kettering Cancer Center and Helsinki nomograms were also tested in our patient population.

Results: Pathologic tumor size greater than 2 cm, the ratio of metastatic SLN to dissected SLN, metastatic tumor greater than 1 cm and tumors that extended outside the SLN's capsule were found to be associated with non-sentinel node metastasis in both univariate and multivariate tests. MD Anderson nomogram performed well with an area under the curve (AUC) value of 0.72.

Conclusion: Our results suggest that ALND should be considered in patients with macrometastatic SLN greater than 10 mm in size, have extracapsular extension, have metastatic SLNs at a rate of more than 50% and whose primary tumor is greater than 2 cm.

Keywords: Breast cancer, sentinel node, non-sentinel node metastasis, nomogram

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Introduction

Although the latest National Comprehensive Cancer Network (NCCN) guidelines are consistent with American College of Surgeons Oncology Group (ACOSOG) - Z0011 trial with regard to omitting axillary lymph node dissection (ALND) in some patients with metastatic sentinel lymph node (SLN), most surgeons still prefer a complete ALND when SLN is found to be positive (1). However, great inspiration by the study mentioned above has led to detailed investigations regarding the dilemma of avoiding ALND even when SLN is positive for tumor metastasis. Some surgical oncology centers conducted prospective studies or revisited their results and tried to apply some well-known nomograms to their patient population and attempted to perfect the current nomograms to safely discard ALND (2-5).

Since ALND is now considered as a staging procedure for breast cancer that bears clinically substantial risks for known morbidities such as restrictions in shoulder joint motions, seroma formation in the armpit, numbness, lymphedema, it becomes a rather invasive intervention for its purpose (6-8). Regarding local control, axillary radiotherapy has shown promise for comparable outcomes with much lower morbidity rates in T_{1-2} tumors (3). Besides, with the knowledge of ALND providing no more useful information on the stage of the disease in about 30-60% of patients, effective strategies should be developed to avoid it when feasible (9-11).

On the grounds of these data, we conducted retrospective analyses of our patients that were found to have positive SLN and underwent consequent ALND. Characteristics of patients, as well as tumors, were interpreted in a manner to lead the way to decide whether to avoid ALND in a subgroup of patients is applicable and three most common used nomograms were checked in our patient population to

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observe their feasibility.

Materials and Methods

The data were probed for breast cancer patients that were operated on between February 2014 and June 2016. SLN biopsies were performed in 507 patients and out of 157 patients who underwent ALND for a metastatic SLN, 151 were found eligible for the analyses as having macrometastatic (>2mm) SLN. None were subjected to any neoadjuvant treatments. SLNs were identified using both Tc-labeled radioactive tracer (nanocolloid) and blue dye (1% methylene blue) that were injected to the site of primary tumor. Radioactivity was detected with a portable gamma probe. The node was defined as sentinel when it was dyed in blue, showed the highest level of radioactivity with regards to adjacent ones or when palpated intraoperatively. When multiple lymph nodes met the above criteria, they were all collected for frozen section examination. Dissected SLNs were studied with frozen section; when found to be positive, ALND was performed in the same session. ALND consisted of the dissection of level I and II axillary nodes. When suspicious nodes were located, they were also included in the specimen regardless of their location. Routine hematoxylin and eosin examination were performed for both ALND and SLN materials postoperatively. Estrogen (ER), progesterone (PR) receptors as well as the Ki-67 and c-erbB-2 status of the tumor was noted. Silver in situ hybridization (SISH) was used to confirm c-erbB-2 status when necessary. Lymphovascular invasion (LVI) in the primary tumor, the size of the metastasis in SLN and presence of extracapsular involvement in the sentinel node(s) were also recorded. ER and/or PR (+), c-erbB-2(-) tumors are defined as Luminal A, whereas ER and/or PR(+), c-erbB-2(+) or c-erbB-2(-) but Ki-6 >15% tumors are considered as Luminal B, and both ER and PR are (-) but c-erbB-2(+) are defined as nonluminal HER2/neu over-expression, and all ER, PR and c-erbB-2(-) tumors are considered as triple negative.

MD Anderson's Breast Cancer Nomogram to Predict Additional Positive Non-SLN without Neoadjuvant Chemotherapy (available online at http://www3.mdanderson.org/app/medcalc/bc_nomogram2/index.cfm?pagename=nsln), Memorial Sloan-Kettering Cancer Center's (MSKCC) Breast Cancer Nomogram: Breast Additional Non SLN Metastases (available online at http://nomograms.mskcc.org/breast/BreastAdditionalNonSLNMetastasesPage.aspx) and Helsinki University Hospital's risk prediction of non-sentinel node metastases after tumor-positive sentinel node biopsy (available for download at http://www.hus.fi/sairaanhoito/sairaanhoitopalvelut/rintarauhaskirurgia/predictive-tools/sivut/default.aspx?redirected=1) nomograms were used to predict non-sentinel lymph node metastasis in our patient population.

Institutional Review Board approval of Ankara Oncology Training and Research Hospital was granted (2016/114).

This study was performed in compliance with the Declaration of Helsinki.

For this type of study, formal patient consent is not required.

This article does not contain any studies with human participants or animals performed by any of the authors.

Statistical Analyses

Statistical analyses were done using the Statistical Package Program software (SPSS®) version 22 (IBM Corp.; Armonk, NY, USA). Categorical data was presented in percentage and comparison between them was done with the Chi-square test. Multivariate analysis was done with logistic regression to predict the independent factors affecting non-sentinel lymph node metastasis. A significant difference was considered when p-value was found to be ≤0.05. Predictive values of three nomograms were checked for calculating the area under curve (AUC) of the receiver operator characteristic (ROC) curve.

Results

Surgical intervention targeting breast lesion was mastectomy in 80 (53%), conventional breast conserving surgery in 27 (18%) and excision with oncoplastic reconstruction (such as inferior and superior pedicle mammoplasties, etc.) in 44 (29%) of patients. Mean size of primary tumors was 27.9 mm, ranging from 6 mm to 70. Upon pathologic examination, 142 (94%) of tumors were infiltrating ductal carcinoma, 4 (2.6%) were in purely lobular type and 5 (3.3%) were mixed or other pathologic types. Tumors were mostly located in the outer upper quadrant of the breast (n=105, 69.5%). Multifocal tumors were detected in 26 patients (17.2%). Other characteristics of 151 patients and tumors are summarized in Table 1.

Table 1. Patient and tumor characteristics

Patient and Tumor Characteristics		n (%)
Age	<50	58 (38.4)
	≥50	93 (61.6)
Pathologic Tumor Size	T1	38 (25.2)
	T2	105 (69.5)
	T3	8 (5.3)
Tumor		
Grade	I	8 (5.3)
	II	67 (44.4)
	III	76 (50.3)
ER	Positive	124 (82.1)
	Negative	27 (17.9)
PR	Positive	121 (80.1)
	Negative	30 (19.9)
C-erb-B2	Positive	46 (30.5)
	Negative	105 (69.5)
Molecular subtype	Luminal A	25 (16.6)
	Luminal B	104 (68.9)
	Triple (-)	15 (9.9)
	Her2 - overexp.	7 (4.6)
LVI	Present	56 (37.1)
	Absent	95 (62.9)
Extracapsular Extension	Present	108 (71.5)
	Absent	43 (28.5)

ER: Estrogen Receptor; PR: Progesterone Receptor; LVI: Lymphovascular Invasion

The size of metastatic sentinel lymph nodes ranged between 3-40mm (mean 12.6mm) and all had macrometastatic disease (>2mm). Descriptive statistics regarding axillary lymph nodes are given in Table 2.

Among many variables tested, four of them showed statistical significance: pathologic tumor size greater than 2cm, the ratio of metastatic SLN to dissected SLN, metastatic tumor greater than 1 cm and tumors extending outside the SLN capsule. Univariate analyses of variables are summarized in Table 3.

All factors mentioned above that affect the non-sentinel lymph node involvement kept their significance on multivariate analysis. The multivariate analysis to analyze the independent factors associated with non-sentinel lymph node involvement is shown in Table 4.

The AUC values for MD Anderson, Helsinki and MSKCC nomograms were 0.72, 0.65, and 0.64, respectively (Figure 1).

Discussion and Conclusion

With the knowledge of axillary dissection's complicative nature, efforts are concentrated on avoiding it when applicable. Accurate prediction of metastases to axilla beyond sentinel node(s) is the focus of interest regarding the prevention of unnecessary ALND. This gained more importance with reports stating that 40-70% of patients with positive SLN have further metastasis in the remaining axilla, making ALND superfluous in almost half of them (9-11). Non-sentinel lymph node metastasis was absent in 60 of our patients (39.7%) placing them in the unnecessarily performed ALND group.

The age of the patient, pathologic tumor size, grade, histology, multifocality, hormone receptor status, Ki-67 and c-erbB-2 expression and LVI are found to be related to non-sentinel node metastasis in previous studies (12-16). Among those tumor-related parameters, only tumor size is found to be associated with non-sentinel node involvement in our series.

The number of sentinel lymph nodes dissected and the ratio of metastatic/dissected sentinel nodes, tumor burden in metastatic sentinel node and extracapsular invasion to the surrounding tissue were investigated using both univariant and multivariant analyses and found related with non-sentinel lymph node involvement in various studies (17-22). Considering our findings, it can be stated that when more than half of the dissected sentinel nodes are infiltrated, the likelihood of having metastasis in the rest of the axillary lymph nodes significantly increases. Metastatic SLN greater than 10 mm in size is found to pose a risk for non-sentinel node involvement according to our findings. Furthermore, the strongest correlation was found between extracapsular extension of the tumor in the SLN with a hazard ratio of 13.8 (Table 4).

Table 2: Descriptive statistics of axillary lymph nodes

	Minimum	Maximum	Median
Dissected SLN (n)	1	9	2
Metastatic SLN (n)	1	7	1
Metastatic SLN size (mm)	3	40	11
Ratio of metastatic/ dissected SLNs (%)	11	100	60
Dissected ALN1 (n)	7	45	19
Metastatic ALN1 (n)	0	36	1

SLN: sentinel lymph node; ALN: axillary lymph node

Table 3: Univariate analysis of the data

Variable	p (2-sided)
Age <50 vs. ≥50	0.124
Pathologic tumor size ≤2cm vs. >2cm	0.014
Pathologic tumor size T1-T2-T3	0.235
Histopathology of the tumor IDC, ILC, mixed and other	0.692
Grade I-II-III	0.986
ER positive vs. negative	0.167
PR positive vs. negative	0.157
c-erb-B2 positive vs. negative	0.391
Ki-67 <15 vs. ≥15	0.271
LVI Present vs. absent	0.086
Multifocality Present vs. absent	0.534
Ratio of metastatic/dissected SLN's ≤50% vs. >50%	0.005
Metastatic SLN size <10mm vs. ≥10mm	0.002
Extracapsular extension Present vs. absent	0.0001

ER: estrogen receptor; PR: progesterone receptor; LVI: lymphovascular invasion

Table 4: Multivariate analysis of factors affecting non-sentinel node metastasis

		95% Confidence Interval		Odds
Variable	p	lower	upper	Ratio
Tumor Size ≤2cm vs. >2cm	0.043	1.018	5.626	5.2
Ratio of metastatic/ dissected SLN's ≤50% vs. >50%	0.038	1.037	4.521	7.4
Metastatic SLN size <10mm vs. ≥10mm	0.045	1.014	4.910	5.6
Extracapsular extension Present vs. absent	0.005	1.372	9.458	13.8

SLN: sentinel lymph node

Öz et al. (25) reported that Ki-67 and c-erb-B2 expression is connected with non-sentinel metastasis and also two other studies stated c-erb-B2 as an independent factor (23, 24). We found no direct relation between Ki-67, c-erb-B2, hormone receptor status and non-sentinel involvement. Molecular subtypes are thought to influence the spread of the disease regionally. Zhou et al. (26) reported that both luminal A and B subtypes were riskier in terms of non-sentinel node metastasis. Gülben et al. (27) also found luminal B subtype was associated with non-sentinel node involvement. However, both studies grouped tumors considering the Ki-67 expression rate. We categorized tumors according to their Ki-67 expression rate and found no relation regarding non-sentinel node metastasis.

Some of the aforementioned factors were used in combination to constitute nomograms like MD Anderson, MSKCC, and Helsinki (21, 28, 29). These three nomograms are widely used in research studies and readily accessible. When the MD Anderson, MSKCC, and Helsinki nomograms were applied, only the MD Anderson nomogram passed the generally accepted threshold for discrimination with an AUC value of 0.72. Helsinki and MSKCC nomograms also did well, but were not powerful enough for our patient population with AUC values of 0.65 and 0.64 respectively.

For patients who do not meet the criteria stated in ACOSOG Z0011 trial, nomograms sound handy in deciding whether to proceed with ALND or not. We tried the three most commonly used, readily available, online and easy-to-use nomograms in our patient population with macrometastatic SLN involvement. Only the MSKCC nomogram did well just above the minimal limit of significance. With our 60% positivity rate on the remaining axilla, it seems far from convenient for us to rely on. However, removing a mean number of 19.6 lymph nodes for clearing a mean number of only 3 metastatic nodes is not acceptable, either. More efforts should be made to rationalize the predictive power of nomograms for non-sentinel node metastasis, especially at the presence of macrometastatic SLN. The more variables are taken into account, the more powerful a nomogram may become.

Until alternative therapies are proven to be as effective as ALND, for patients that do not meet the criteria of ACOSOG Z0011, we prefer to complete the dissection of axilla when faced with metastasis in the SLN.

Ethics Committee Approval: Ethics committee approval was not requested for this study.

Informed Consent: Informed consent was not requested for this study.

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Original Article

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Sub-classification of Breast Masses by Fine Needle Aspiration Cytology

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ABSTRACT

Objective: The aim of this study is to evaluate the accuracy of sub-classification of breast diseases using Fine Needle Aspiration cytology (FNAC).

Materials and methods: A one-year prospective study of 180 consecutive patients with palpable breast lesions who underwent FNAC and subsequently open surgical biopsy for histological confirmation. FNAC was used to sub-classify breast lesions and then correlated with histological diagnosis.

Results: A total of 180 patients were enrolled into the study but only 110 patients with histology report were used for test validity. Seventeen (15.5%) smears were C1; while 46 (41.8%), 5 (4.5%), 4 (3.6%) and 38 (34.6%) were C2, C3, C4 and C5, respectively. FNAC achieved sensitivity of 90.0%, specificity of 95.5%, false positive rate of 5.3%, false negative rate of 8.7%, positive predictive value of 94.7%, negative predictive value of 91.3% and overall diagnostic accuracy of 92.9%. Only 86 (78.2%) of the 110 smears could be sub-classified into different disease conditions of the breast on cytology. FNAC accurately sub-classified 25(78.1%) of fibroadenoma and 28(87.5%) of invasive ductal carcinoma.

Conclusion: FNAC can reasonably sub-classify fibroadenoma, invasive ductal carcinoma and mastitis but there is still a challenge with lobular carcinomas, metaplastic carcinomas, papillary carcinomas and fibrocystic changes.

Keywords: Cytology, breast masses, sub-classification.

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Introduction

Breast lump is one of the commonest presentations of breast diseases. The diagnosis of breast diseases can be achieved like in other clinical conditions using: history, physical examination and investigation which include cytological or histological confirmation. Currently, several studies have advocated the use of 'Triple test' which consists of clinical examination, radiologic examination and cytopathology as more accurate means of making diagnosis of breast lesions (1-5). When all the three components are positive, diagnostic accuracy approaches 100% for malignancy (2). Fine Needle Aspiration cytology (FNAC) is widely used and accepted as a reliable method of making initial pre-operative diagnosis in breast diseases (2, 6). It has been credited with a lot of advantages such as: high accuracy, cheap, fast, out-patient procedure reducing pressure on theatre load, high patient acceptability, and low complication rate (2, 6).

Fine Needle Aspiration cytology reports are classified into 5 categories based on the National Health Services Breast Screening Programme (NHSBSP) of Britain (7). The use of these standardized diagnostic categories is necessary to enhance communication within a multi-disciplinary team and for comparing results from other Centres. The diagnostic categories and their corresponding numerical codes are: Inadequate/insufficient (C1); Benign (C2); Atypical/indeterminate (C3); Suspicious of malignancy (C4) and Malignant (C5). However, Specimen from FNAC can be used to sub-classify breast lesions (7-9). Most studies on FNAC do not make attempt at sub-classifying breast lesions into definite disease types because of the challenges usually encountered (8, 9). The aim of this study is to evaluate the accuracy of sub-classification of breast diseases using FNAC in our Centre.

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Materials and Methods

This is a one-year prospective study of all the consecutive patients with palpable breast lesion presenting at the two general surgery out-patient clinics of the University Teaching Hospital. Approval was sought from the Ethical committee of the University Teaching Hospital before the commencement of the study. The procedure was duly explained to the patients, and that the lump will be removed for histology after the FNAC. Their informed written consent was obtained. Patients who had FNAC were followed up until the histology report was obtained following open surgical biopsy.

Patient lies supine on a couch after exposure of the upper half of the body. The surgeon after washing hands with soap and water wears a pair of surgical gloves. The skin of the breast over the lump was disinfected using gauze soaked in 75% methylated spirit. The dominant hand was used to handle the syringe with 25G needle in place. The other hand was used to stabilize the tumour within the breast. The needle on the syringe was then advanced into the tumour and negative pressure was generated by pulling on the plunger and maintaining the pressure with the fingers and thumb. The needle was moved in and out in different directions in the tumour while maintaining the negative pressure. The movement of the needle continues until adequate material appears in the hub of the needle. The negative pressure was released and the needle withdrawn from the breast. The syringe was separated from the needle, filled with air, re-attached to the needle and its content expressed onto the centre of the microscope slides (wet and dry). Smears were made by spreading the aspirate using another clean slide placed at 45 degree and running it over the slide. The wet slide was fixed by putting it into a Coplin jar containing 95% ethanol while the dry slide was fixed by air-drying (for at least 5 minutes). The two groups of slides were then transported to the laboratory for staining and cytology reporting. If material aspirated was insufficient, further needle passes were done. If the lump is cystic, the entire cyst was completely aspirated, labelled and sent to laboratory for centrifuging and further processing. Residual masses after cyst aspiration were handled like other solid masses.

The wet slides were stained with Papanicolaou staining technique while the dry slides were stained using May-Grunwald-Giemsa staining technique. The patients were also worked up for open surgical biopsies and the samples collected from each patient was immersed in a container with 10% formalin and transported to the histopathology laboratory for preparation and reading.

The cytology and histology reports were documented in the pro-forma used for the study when they were ready. The cytological diagnoses were categorized into one of the five diagnostic categories according to the recommendations of the United Kingdom National Health Services Breast Screening Programme (NHSBSP) (7). The breast samples from FNAC were further sub-classified into definite breast disease entities. The final histopathological diagnosis of each case was then compared with the cytological diagnosis.

The data were entered into a database and statistical analyses carried out using the Statistical Package for Social Sciences (SPSS) version 17.0. (SPSS Inc. Released in 2008; SPSS Statistics for Windows, Version 17.0. Chicago, USA). The results were presented in frequency tables and cross tabulations.

Results

A total of 180 patients were enrolled into the study. All had clinical evaluation as well as FNAC. Only 113 patients had open biopsy with Histology report. Sixty-seven patients defaulted from open surgical biopsy due to one reason or another. The above finding gives a biopsy rate of 63% and default rate of 37%. Only patients who had open biopsy with histology reports were further evaluated. Out of the 113 patients with histology report, two showed normal breast tissues and another one, inadequate specimen. Of the two cases of normal histology, one was C4 and the other C1 on FNAC while the case with inadequate specimen on histology was C5 on FNAC. The three were further excluded leaving only 110 patients who were used in the comparative aspect of the study, and to test validity.

Thirty-eight (34.6%) smears were unequivocally malignant (C5) while 46 (41.8%) were benign (C2) i.e. negative for malignant cells. Five (4.5%) smears were probably benign (C3) while 4 (3.6%) smears were suspicious for malignancy (C4). Seventeen (15.5%) smears were unsatisfactory/inadequate (C1) giving an unsatisfactory rate of 15.5%.

Out of the 38 cases that were positive for malignancy on cytology, 36 of them were true positive and two were false positive. Out of 46 cases that were benign on cytology, 42 were true negative while four were false negative. Out of the 17 unsatisfactory cases on cytology, nine were benign on histology while eight were malignant. Three out of the five cases that were probably benign on cytology were confirmed benign on histology while two were confirmed malignant. Out of the four cases suspicious for malignancy on cytology, two were benign on histology while two were confirmed malignant (Table1).

Diagnostic validities of FNAC when both unsatisfactory and suspicious smears are excluded is shown in Table 2.

Table 1: Cytology report/ Histology type

		Histology type		
		Benign	**Malignant**	**Total**
Cytology	Unsatisfactory(C1)	9	8	17
report	Benign(C2)	42	4	46
	Probably benign(C3)	3	2	5
	Probably malignant(C4)	2	2	4
	Malignant(C5)	2	36	38
Total		58	52	110

Table 2: Diagnostic validities of FNAC excluding unsatisfactory and suspicious smears

Diagnostic validity	**Value in percentage**
Sensitivity	90.0
Specificity	95.5
False positive rate	5.3
False negative rate	8.7
Positive predictive value	94.7
Negative predictive value	91.3
Overall diagnostic accuracy	92.9

FNAC: Fine Needle Aspiration cytology

Table 3: Sub-classification of cytology results

Frequency	Percent	
Fibroadenoma	32	29.1
Invasive lobular ca	1	.9
Invasive ductal ca	32	29.1
Mastitis	2	1.8
Fibrocystic change	8	7.3
Fat necrosis	3	2.7
Benign proliferative lesion	2	1.8
Benign cystic lesion	2	1.8
Metaplastic ca	3	2.7
Papillary ca	1	.9
Unclassified	24	21.8
Total	110	100.0

Only 86 (78.2%) of the 110 smears could be sub-classified into different disease conditions of the breast on cytology. Twenty-four (21.8%) smears could not be sub-classified. Out of the 86 smears sub-classified, fibroadenoma was 32 in number and invasive ductal carcinoma was also 32 in number. The rest of the sub-classes are shown below (Table 3).

Out of the 32 diagnosis of fibroadenoma on FNAC, histology confirmed: 25 (78.1%) to be fibroadenoma, five (15.6%) to be fibrocystic changes and one (3.1%) each of invasive ductal carcinoma and mastitis. Also, out of another 32 diagnosis of invasive ductal carcinoma by FNAC, histology confirmed: 28 (87.5%) of them to be invasive ductal carcinoma and the remaining 4 (12.5%) to be metaplastic carcinoma.

Discussion

Fine needle aspiration cytology (FNAC) was found to be more specific than sensitive in this study, 95.5% and 90.0%, respectively with overall diagnostic accuracy of 92.9% (Table 2). These values are comparable to those documented in similar studies (10-14) and much higher than >60% for specificity and > 80% for sensitivity recommended by NHSBSP of Britain (7). The high values for sensitivity, specificity and overall diagnostic accuracy obtained in this study may be due to the fact that only palpable lumps were sampled and the fact that most of the patients presented late with large lumps. With sensitivity of 90.0% in this study, it means that the diagnosis of malignancy can be made about 90% of the times by FNAC. Also with specificity of 95.5% obtained in this study, it means that FNAC can exclude malignancy in about 95.5% of the cases. And with overall diagnostic accuracy of 92.9%, it shows that FNAC can make diagnosis of both benign and malignant diseases in about 92.9% of the cases.

Apart from telling whether a lesion is benign or malignant, FNAC can significantly sub-classify breast lesions into definite histological entities. According to the study by Young et al (8), FNAC of the breast is a reliable method for the diagnosis of breast carcinoma but difficulties still exist in their ability to determine tumour sub-type. In the above study, performance was best for the diagnosis of adenocarcinoma (ductal type) with 65% accuracy. The rates for exact diagnosis of lobular, medullary and mucinous carcinomas were 20%, 12%, and 27%, respectively.

In the current study, only 86 (78.2%) of the 110 smears could be sub-classified into different histological conditions of the breast on cytology. Twenty-four (21.8%) smears could not be sub-classified. Out of the 86 smears sub-classified by FNAC, fibroadenoma was 32 in number and invasive ductal carcinoma was also 32 in number. Correlation of FNAC sub-classification with histopathology results showed that: out of the 32 diagnoses of fibroadenoma on FNAC, histology confirmed: 25 to be fibroadenoma giving an accuracy of 78.1%, five to be fibrocystic changes and one each of invasive ductal carcinoma and mastitis. Also, out of another 32 diagnoses of invasive ductal carcinoma by FNAC, histopathology confirmed: 28 of them to be invasive ductal carcinoma with an accuracy of 87.5% and the remaining four to be metaplastic carcinoma. Three diagnoses of metaplastic carcinoma on FNAC proved to be two invasive ductal carcinomas and one metaplastic carcinoma on histopathology. Also, a diagnosis of papillary carcinoma on FNAC was confirmed invasive ductal carcinoma on histopathology. One diagnosis of lobular carcinoma on FNAC proved to be mastitis on histopathology. Two cases of mastitis on FNAC were accurately diagnosed as mastitis on histopathology. Also, out of the eight cases of fibrocystic changes by FNAC, four were fibrocystic changes while three were invasive ductal carcinoma and one adenosis on histopathology (Table 3).

The accuracy of FNAC in this study to sub-classify breast diseases was comparable to that by Young et al (8) in their study on diagnosis and sub-classification of breast carcinoma by FNAC. The current study however achieved higher accuracy of 87.5% compared to 65% by Young et al (8) for invasive ductal carcinoma. However, making accurate diagnosis of metaplastic carcinoma, papillary carcinoma, lobular carcinoma and fibrocystic changes is still a problem. Maygarden et al (9) in their study on sub-classification of benign breast disease by fine needle aspiration cytology, comparing cytological and histopathological findings in 265 palpable breast masses found that overall, the specific diagnosis was correct in 80% of cases. This is comparable to the accuracy of 78.1% for fibroadenoma obtained in the current study. Also, in another study by López-Ferrer et al (15) on Fine needle aspiration cytology of breast fibroadenoma, correlating the cytopathology and histopathology of 405 cases, cytohistological agreement was present in 287 of the 362 cytodiagnoses. This ensured the sensitivity of the cytological diagnosis of Fibroadenoma to be 86.9% with a positive predictive value of 79.3%. This is slightly higher than the value obtained in this present study.

Only 113 of 180 patients initially recruited for the study presented for open surgical biopsy and histopathology. Sixty-seven patients defaulted for some reasons and that formed a major limitation for the study.

Conclusion

Fine needle aspiration cytology can reasonably sub-classify fibroadenoma, invasive ductal carcinoma and mastitis but there is still a challenge with lobular carcinoma, metaplastic carcinoma, papillary carcinoma and fibrocystic changes.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University Teaching Hospital.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.I.M., C.O.U., S.N.C.A., G.U.C., I.V.O., D.C.D.A.; Design - C.I.M., C.O.U., S.N.C.A., G.U.C., I.V.O., D.C.D.A.; Supervision - C.I.M., C.O.U., S.N.C.A., G.U.C.; Resources - C.I.M., C.O.U., S.N.C.A., G.U.C., I.V.O., D.C.D.A.; Materials - C.I.M., C.O.U., S.N.C.A., G.U.C., I.V.O., D.C.D.A.; Data Collection and/or Processing - C.I.M.; Analysis and/or Interpretation - C.I.M.; Literature Search C.I.M.; Writing Manuscript - C.I.M., C.O.U.; Critical Review - C.I.M., C.O.U., S.N.C.A., G.U.C., I.V.O., D.C.D.A.

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APPENDIX

APPENDIX A: Diagnostic category:

1. Inadequate/insufficient (C1): This category is used when the smears are too sparsely cellular or distorted to allow a microscopic diagnosis or the aspirate is inconsistent with the clinical and image findings. Since this is a subjective diagnosis an explanation of why the sample is inadequate/insufficient should be given.
2. Benign (C2): This diagnostic category is used when the sample is adequate and shows no evidence of malignancy.
3. Atypical/indeterminate (C3): This category is used when smears with benign features also show features which may be seen with malignancy, such as loss of cohesion or nuclear atypia. Another possible circumstance includes a lesion in which the cellularity is low with subtle cytological atypia. Aspirate showing papillary features or having mucin may also be placed in this category, depending on the circumstances.
4. Suspicious of malignancy (C4): This diagnostic category is used when the smears show features suggestive of but not diagnostic of malignancy. The malignant cells may be too scanty, obscured by artefact or show atypical features more marked than in the atypical or indeterminate category but not diagnostic of malignancy.
5. Malignant (C5): This diagnostic category is used when the aspirate is clearly malignant. This diagnostic category includes invasive breast carcinoma, ductal carcinoma in-situ and other malignancies.

APPENDIX B: Conditions associated with false positive diagnosis in FNAC:

False positive diagnosis in FNAC is frequently due to difficulties with interpretation. Some of the conditions associated with false positive diagnosis include:

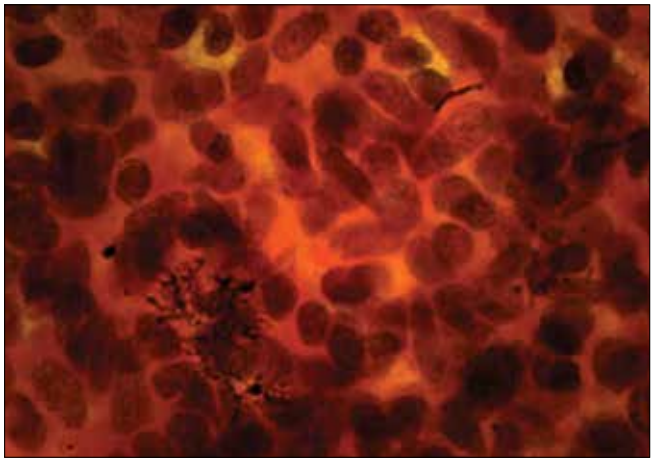
1. Fibroadenoma with atypical features.
2. Mass or thickening associated with lactation.
3. Radial scar with hyperplasia.
4. Papilloma: It is usually impossible to reliably differentiate between papilloma, atypical papilloma, intra-cystic papillary carcinoma and invasive papillary carcinoma based on cytology material alone.
5. Radiation changes: Radiation induced epithelial atypia is common in benign breast tissue after treatment. Similar problem may arise following chemotherapy.
6. Fat necrosis: Triple test here may be misleading as fat necrosis can mimic carcinoma both clinically and on imaging.
7. Atypical apocrine cells: Differentiating apocrine metaplasia and apocrine carcinoma can occasionally be difficult.
8. Gynaecomastia.
9. Phyllodes tumour.
10. Adenomyoepithelioma.
11. Tubular adenoma.
12. Granular cell tumour.

APPENDIX C: False negative diagnosis in FNAC:

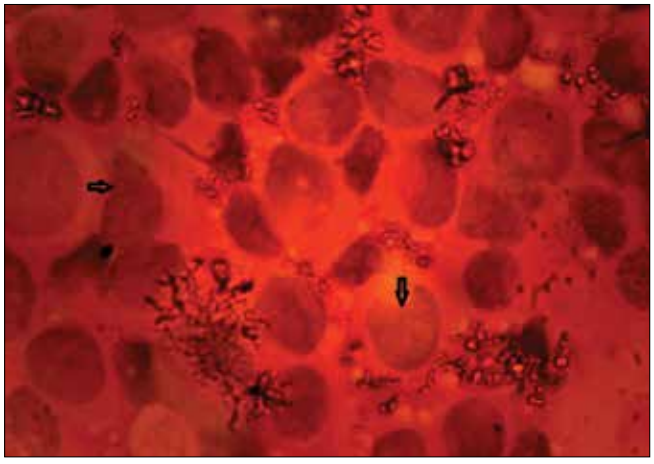
False negative diagnoses are most commonly as a result of sampling error and at times due to interpretation error. Some of the situations and conditions associated with false negative diagnoses in FNAC include:

1. Difficulty in sampling some lesions, for example: small malignant lesions that are well differentiated and sclerotic, masses that are difficult to feel and lesions close to the chest wall.
2. Well differentiated grade I cancer, as cell yield may be poor or only have mild cellular atypia.
3. Infarcted papilloma.
4. Invasive lobular carcinoma may yield only few cells.
5. Low grade ductal carcinoma in-situ, some tubular carcinoma and cribriform carcinoma my yield deceptively 'benign' aspirates.
6. Inflammatory carcinomas, no definite mass may be palpable.
7. Necrosis in the centre of a high grade carcinoma.
8. Sclerosis which is a potential cause of a low cell yield.
9. Papillary carcinomas which requires excision and examination of the whole lesion and capsule.
10. Mucinous tumours are often well differentiated and the cell yield may be poor.

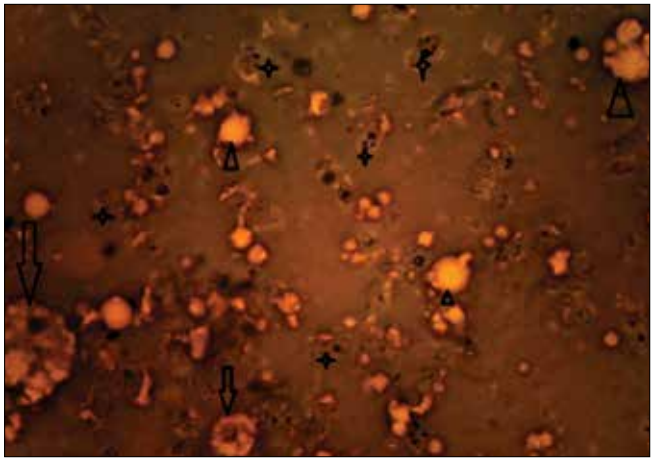
APPENDIX D: Photomicrograph of common breast diseases:



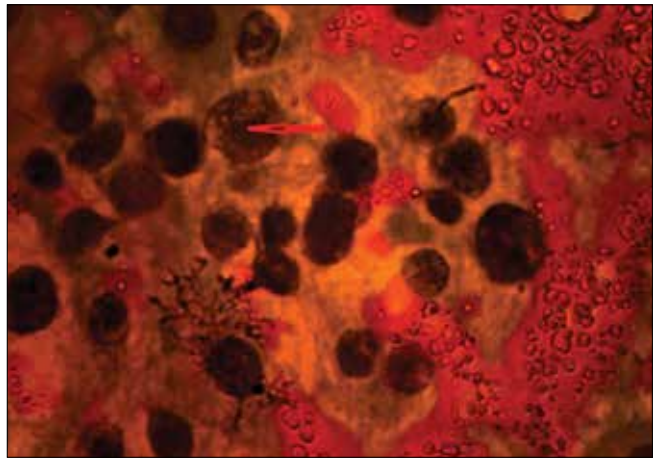
Photomicrograph of fibroadenoma {x1000 magnification; Papanicoloua Stain}:-. At this magnification ductal cells with bland nuclear features admixed with myoepithelial cells can be appreciated.



Photomicrograph of metaplastic carcinoma of breast (x1000 magnification; Papanicoloua Stain):- At this magnification highly pleomorphic nuclei with irregular nuclear margins are depicted by the two arrows can be appreciated.



Photomicrograph of fibrocystic changes {x400 magnification; giemsa stain):- In the background are many foamy macrophages, fat droplets and neutrophil polymorphs as depicted by arrows, arrowheads and stars, respectively.



Photomicrograph of invasive ductal carcinoma, not otherwise specified {x400 magnification; Papanicoloua Stain}:-At this magnification the loose cluster of tumour cells is seen to be composed of neoplastic ductal cells with pleomorphic hyperchromatic nuclei and abundant granular cytoplasm. Some of the cells contain prominent nucleoli as depicted by the arrow.

Original Article

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Porcine Dermal Collagen Prevents Seroma Formation After Mastectomy and Axillary Dissection in Rats

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ABSTRACT

Objective: Seroma occurs as a result of accumulation lymphovascular liquid in the dead space forming after tissue dissection. It is the most common complication after breast surgery. Collagens are the common component of extracellular matrix and have an important role in wound healing. In this study, we aimed to investigate the efficiency of the Porcine Dermal Collagen in preventing Seroma.

Materials and methods: Eighteen young female Wistar rats were used and divided into three groups. Mastectomy and axillary dissection were performed in each group. No other procedures were performed in Group 1 (Control group). Porcine dermal collagen was applied to 50% of the mastectomy field in Group 2 and to 100% of the mastectomy field in Group 3.

Results: Seroma volume was significantly decreased in Group 3 in contrast to Groups 1 and 2 ($p<0.001$) and in Group 2 in contrast to Group 1 ($p<0.001$). Vascular proliferation, granulation tissue formation and congestion were significantly increased in Group 3 ($p<0.05$).

Conclusion: We conclude that the use of Porcine Dermal Collagen reduces the formation of seroma in the model of experimental mastectomy and axillary dissection. As the amount of Porcine Dermal Collagen applied increases the formation of seroma reduces.

Keywords: Axillary Dissection, breast, mastectomy, porcine dermal collagen, seroma

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Introduction

Seroma occurs as a result of leakage of the lymphovascular fluid into the dead space forming after tissue excision or dissection. It is the most common complication after breast cancer surgery. The incidence varies between 10-50% (1-3). In breast cancer surgery, it occurs most frequently after modified radical mastectomy and axillary lymph node dissection (4).

It can cause many problems such as prolonged hospitalization time, wound infection and delay adjuvant treatment. There is no agreement on the prevention of seroma in breast cancer surgery.

Porcine Dermal Collagen is a non-allergenic, nontoxic material which is structurally similar to human dermis and is often used for the repair of the abdominal wall defects. It is produced from acellular pig matrix and does not cause foreign body tissue reaction. Its 3-dimensional collagenous architecture increases fibroblast infiltration, fibroblast growth and neovascularization (5-8). It has been shown that in contrast to other materials, seroma occurs less frequently in abdominal wall repair when Porcine dermal collagen-containing materials are used (6, 9).

Porcine dermal collagen temperately increases inflammatory process. After implantation, granulocytes are dominant in first 48 hours. In 7 days, monocytes/macrophages and a lesser number of natural killer cells become dominant in the infiltrate. These cells activate expression of cell surface adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and CD11b. It is known that these adhesion molecules have a critical role in increasing inflammatory response (6).

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In this study, we aimed to show the effect of Porcine Dermal Collagen on preventing Seroma through its characteristics such as 3-dimensional structure, being a component of normal human tissue and being inert and increasing adhesion.

Materials and Methods

The approval of the study was obtained from the local Ethical Committee of the Experimental Animal Laboratory. Eighteen female Wistar rats at the average weight of 200-250 grams (g) were used in the study. We divided the rats into 3 groups and each group included 6 rats. All the rats were fed with standard laboratory diet and tap water, and observed under controlled conditions of temperature (22±2 centigrade degree) and light with 12 hours day/night cycle.

Unilateral (right) mastectomy and axillary dissection were performed in all rats by the method described by Harada et al. (10). Prophylactic antibiotics were used in none of the groups. For anesthesia, 50 milligram (mg), kilogram (kg) intraperitoneal ketamine (Ketalar®, Parke Davis and Co. Inc., Detroit, Michigan, United States of America) and 5 mg/kg intramuscular xylazine (Rompun®, Bayer, Leverkusen, North Rhine-Westphalia, Germany) were used. After that, the anesthesia rats were fixed to operation desk with plaster. Their anterior chest wall and right axillary region were shaved with lancet and cleaned with 10% povidone-iodine solution.

After a vertical incision extending from the jugular notch to the xiphoid, a flap formed by the cutaneous and subcutaneous tissue was lifted from the chest wall. The major pectoralis muscle was dissected up to the level of the latissimus dorsi muscle, freed, and then excised. All the axillary lymph nodes were excised while preserving the integrity of the axillary artery, veins, and nerves.

The dissection area was measured (Figure 1, 2). The average dissection area was found to be 3 cm². After mastectomy and axillary dissection, no additional procedures were performed in the control group (Group 1). Porcine dermal collagen was postoperatively applied to 50% of mastectomy area in Group 2 and to 100% of mastectomy area in Group 3 (Figure 3, 4, 5, 6). After hemostatic control was established, the skin was closed with 2.0 silk sutures in all groups.

Figure 1. Measuring of dissection area after mastectomy and axillary dissection (Average dissection area is 3 cm²)

The rats were observed for 10 days after the operation. On post-operative Day 10, seroma fluid was aspirated with sterile injectors from the surgical site under ketamine anesthesia, and the total volume in milliliters was recorded. Tissue samples were obtained from the skin, axilla and chest wall in the surgical area for histopathologic examination and all the samples were placed in 10% formaldehyde solution. The rats were sacrificed with high dose ether anesthesia at the end of all procedures.

The tissue samples were embedded in paraffin blocks after the tissue processing, 5-micrometer sections were taken from each block and stained with hematoxylin-eosin (HE). Hemorrhage, edema, conges-

Figure 2. Measuring of dissection area after mastectomy and axillary dissection (Average dissection area is 3 cm²)

Figure 3. Cutting the porcine dermal collagen to cover 50% of the dissection area

Figure 4. Cutting the porcine dermal collagen to cover 100% of the dissection area

Figure 5. Applying porcine dermal collagen to 50% of dissection area

Figure 6. Applying porcine dermal collagen to 100% of dissection area

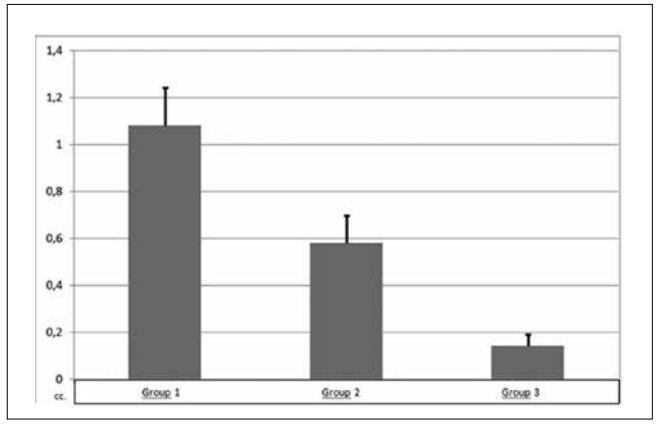
tion, polymorphonuclear leukocytes, growth of fibrous tissue, fibroblasts, lymphocytes, macrophages, granulation tissue, vascular proliferation and necrosis were evaluated qualitatively under light microscope. Cellular and histopathological data were scored semi-quantitatively in 0 to 3+scale as 0=absent, 1=mild, 2=moderate, and 3=marked.

Statistical analyzes were performed with Microsoft Windows Excel 2007 program. The volumes of seroma were statistically evaluated by ANOVA and Multiple Comparison Procedures (Holm-Sidak method). Histopathological parameters were statistically evaluated by Kruskal-Wallis One Way Analysis of Variance on Ranks method and Tukey tests.

Results

Neither complications such as wound infection, wound clefting nor flap necrosis were seen in any rats and nor any of them died during the course of the experiment. The mean seroma volumes were 1.083 cc (±0.16 cc) in the control group (Group 1), 0.583 cc (±0.11 cc) in Group 2 (50% porcine dermal collagen mesh implantation group) and 0.142 cc (±0.05 cc) in Group 3 (100% porcine dermal collagen mesh implantation group) respectively. Seroma volume was significantly lower in Group 3 in contrast to Group 1 and 2 ($p<0.001$) and in Group 2 in contrast to Group 1 ($p<0.001$) (Graphic 1).

Vascular proliferation and granulation tissue formation were significantly higher in Group 3 in contrast to Group 1 and 2 ($p<0.05$); there was no significant difference between Groups 2 and 1 ($p>0.05$)(Figure 7). The congestion was found to be significantly higher in Group 3 in contrast to Group 1 and 2 ($p<0.05$). There was no significant difference in hemorrhage, macrophage, neutrophil, lymphocyte parameters among all the groups. Despite the fact that we observed more severe



Graphic 1. Mean seroma volumes in each groups. Group 1 = 1.083cc. (±0.16 cc.); Group 2 = 0.583cc.(±0.11 cc.); Group 3= 0.142 cc. (±0.05 cc.). $p < 0.001$

fibroblasts and fibrous tissue formation in Group 2 and 3, these parameters did not show significance in between all groups.

Discussion and Conclusion

In the literature, several methods have been recommended to reduce seroma formation by this time. These methods can be separated into 2 groups. The first group of these methods intends to prevent the dead space occurring after surgery.

Aitken et al. (11) concluded that seroma formation was reduced with the method of flap fixation by sutures. In the study where external

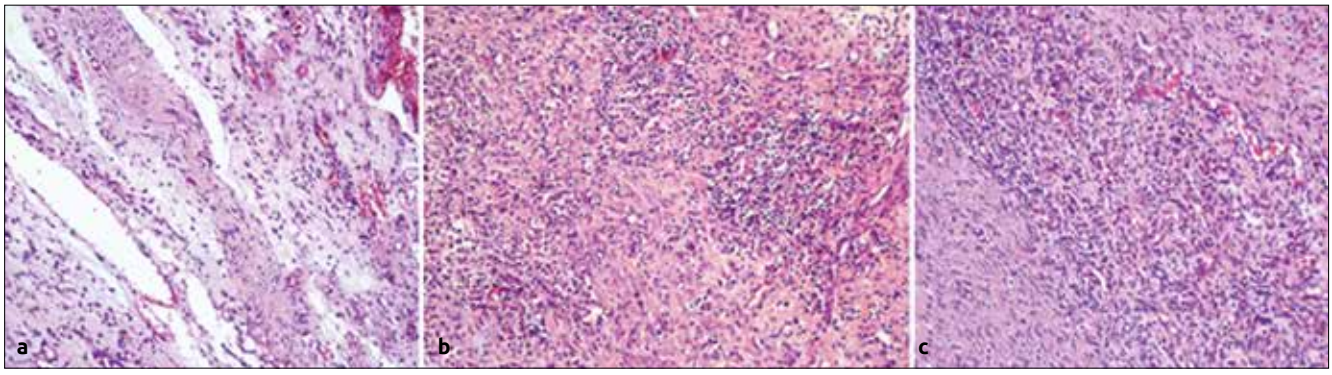


Figure 7. Vascular proliferation and granulation tissue in Group 1(a), Group 2(b) and Group 3(c)

Table 1: The experimental studies in which sclerosing agents were used

Researchers	Experimental subject	The agent used	Mean seroma volume in control group	Mean seroma volum in study group
Silverman et al.	Sprague-Dawley rat (280-320 gr)	Poliethylene oxide dimethacrylate	3.25 cc	0.37 cc
Wang et al.	Sprague- Dawley rat (280-320 gr)	Light-activated Fibrin glue	4.2±2.9 cc	1.1 ±1.6 cc
Lindsey et al.	Sprague- Dawley rat (280-320 gr)	Fibrin glue	1.1-4.3 cc	1.8-2.4 cc
Menon et al.	Sprague- Dawley rat (280-320 gr)	Albumin-Gluteraldehyde	5.19±3.65 cc	0.25±0.43cc.
Koçdor et al.	Sprague- Dawley rat (280-320 gr)	Corynebacterium parvum	1.4 cc	0.3 cc
Eroglu et al.	Male guinea pigs (480-900 gr)	Fibrin glue	4- 6.8 cc	1.3 cc
Koçdor et al.	Wistar rat (215.2gr)	Fluorouracil	1.04 cc	0.3 cc

compression method and flap fixation method were compared after breast surgery, Kuroi et al. (12) showed that seroma formation was lower in the group of patients for whom flap fixation method was applied by using sutures. Bonnema et al. (13) compared low pressure vacuum system and high pressure vacuum system and found that body mass index was directly related to seroma formation but negative pressure vacuum and postoperative arm and shoulder movement restrictions were not related to seroma formation.

The second group of methods intends to reduce the formation of seroma. The agents used for this purpose are as follows: sclerosing agents (Fibrin glue, Tetrasycline, Hidrocloric acide, Microporous Polysaccharide spherules, Iodized talc), anti-inflammatory drugs (Acetyl salicylic acid, Nonsteroidal anti-inflammatory drugs), chemotherapeutic agents (Fluorouracil, Mytomycin-C) and radiotherapy.

These sclerosing agents were used in some clinical and experimental studies. Burak et al. (14) observed that 37% of patients given bovine thrombin showed seroma formation and 40% of the control patients showed seroma formation. In the study by Berger et al. (15), the ratio of seroma formation was 39% in the group that used fibrin glue and 42% in control group. Waddenburn et al. (16) used same agent and found the ratio of seroma formation as being 64% in the study group and 53% in control group.

In the literature, there are also experimental studies in which sclerosing agents such as fibrin glue, Poliethylene oxide dimethacrylate, albumin gluteraldehyde, cornybacterium parvum, 5- Fluorourasil, Microporous Polysaccharide spherules, Myhtilus edilus protein were used. These studies are summarized in Table 1. Experimental studies in which sclerosing agents were used had better outcomes than clinical studies.

After reviewing the relevant literature, it was seen that the studies using sclerosing agents published more successful outcomes than the studies aiming to reduce dead space after surgery. For this reason, a material which could partially reduce dead space and increase fibrosis when it was applied to dissection area was decided to be used in this study.

Porcine dermal collagen is an agent which is used for repair of abdominal wall defects, treatment of burns, pelvic reconstructions, head and face reconstructions. It is a non-allergenic and non-toxic material which is structurally similar to human dermis. Its 3-dimensional structure increases fibroblast infiltration and neovascularization (5-8). In repair of abdominal wall defects, it was seen that seroma formation was lower when porcine dermal collagen was used (6, 9). According to these clinical observations, porcine dermal collagen was chosen in this experimental seroma model.

The significant decrease in seroma volume seen in our study groups is similar to the results of some sclerosing agents such as fibrin glue used by Harada et al. (10), mytilus edilus protein used by Chung et al. (3) and albumin glutaraldehyde used by Menon et al. (17).

The inverse ratio between the seroma volume and the amount of porcine dermal collagen applied to the tissue in our study was also seen in the study of Sanders et al. (18) in which fibrinogen and thrombin concentration was used.

In histopathological examinations, we investigated whether there was any difference in tissue healing between control and study groups and evaluated the effect of porcine dermal collagen on the process of tissue healing.

In pathological samples, no microorganisms were seen, which proved not only that we provided the sterile operation conditions but also that no microscopic wound separation occurred in rats.

Increase in congestion, granulation tissue and neovascularization were seen in Group 3 in contrast to other groups ($p<0.05$). According to the studies in the literature, it was predicted that the 3-dimensional architecture of the porcine dermal collagen would increase fibroblast infiltration into the mesh and in this way there would be increase in fibrous tissue in pathological samples (6-9). But no significance was found in the increase of fibrous tissue ($p>0.05$).

In our study, we detected that the effect of reduced seroma occurred with the increase of neovascularisation and granulation tissue, not with the increase of fibrous tissue as in the studies in which sclerosing agents were used such as the study by Wang et al. (19) who used light-activated fibrin glue and the study by Egeli et al. (20) who used microporous polysaccharide spherules.

The major limitations of our study are as follows: having a limited number of rats in working groups and not having compared the effectiveness of porcine dermal collagen with other agents or acellular dermal matrix derived from human dermis.

In the literature, it was seen that neovascularization was not emphasized in the studies related to seroma. In the light of our results, we are convinced that drugs that increase neovascularization can also be used to repress seroma. Additional experimental and clinical studies are needed to prove this point.

In conclusion, the use of Porcine Dermal Collagen reduces the formation of seroma formation after breast surgery, as the amount of Porcine Dermal Collagen applied is increased the formation of seroma is reduced in parallel. Porcine Dermal Collagen shows its effect on reducing seroma formation by filling in the dead space, increasing the adhesion, neovascularization, granulation tissue and accelerating the wound healing. However, our findings are based on experimental animal research; further clinical studies with using porcine dermal collagen and/or acellular human dermal matrix are needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dokuz Eylül University Faculty of Medicine (30.03.2012/20.2012).

Informed Consent: Informed consent was not requested for this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - C.A., M.A.K.; Design - C.A., A.S.; Supervision - C.A., A.S., M.A.K.; Resources - C.A., T.E.; Materials - C.A., A.A.; Data Collection and/or Processing - C.A., A.A., T.E., S.A.; Analysis and/or Interpretation - C.A., A.A., M.A.K.; Literature Search - C.A., S.A, M.A.K.; Writing Manuscript - C.A., A.S., A.A., M.A.K.; Critical Review - A.S., M.A.K.

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

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Original Article

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Roles of Biopsychosocial Factors in the Development of Breast Cancer

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ABSTRACT

Objective: The aim of this study was to determine the roles of biopsychosocial risk factors in the development of breast cancer.

Materials and methods: This hospital-based case-control study included 491 women with breast cancer (study group) and 512 women who did not have cancer or other serious diseases (control group). Biological, psychological, and social risk factors were compared between the two groups. Data were collected using the semi-structured interview, the Stress Assessment Form, and the Coping Strategy Indicator to assess these factors.

Results: When the significantly different biopsychosocial variables between the study and the control groups were evaluated together, independent breast cancer risk factors were found as follows: a stressor experienced in the last 5 years, age 40 years and older, inadequate social support perception, use of avoidance coping strategy, being a housewife, having a family history of cancer, and having a body mass index ≥25.

Conclusion: This study showed a relationship between breast cancer risk and manageable variables (obesity, stressor and coping strategy, social support, and employment status), age and family history of cancer, which are biopsychosocial factors. Biopsychosocial aspects are becoming a greater part of many different healthcare systems.

Keywords: Breast cancer, coping, psychosocial stress, risk factors, social support

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Introduction

Cancer, a chronic and life-threatening disease, is an important cause of morbidity and mortality. The most common type of cancer diagnosed in women is breast cancer (1). Early recognition of high-risk women is important because of the development of surgical, medical, and oncologic alternatives for breast cancer, every passing year (2). Enlightening factors that contribute to breast cancer to prevent the disease, determine risk groups, and improve early diagnosis or treatment strategies are required.

Even though the etiology of breast cancer was not clearly presented in the past, many epidemiologic risk factor studies have been conducted (3, 4), and many unchangeable and changeable risk factors (lifestyle and psychosocial factors) for breast cancer have been identified. According to some studies, changeable factors are useful for developing preventive strategies for breast cancer (5). However, researching stressful life events independently of factors such as coping style, behavioral pattern, and social support could be a flawed approach. A limited number of studies have examined the effects of these variables on the etiology of breast cancer (5, 6, 7). Socio-economic characteristics as risk factors for breast cancer are also discussed. An opinion suggested that socioeconomic characteristics could be an independent risk factor for breast cancer. Another aspect affecting life style such as reproduction and nutrition may be associated with risk of breast

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cancer (8). Several studies have researched risk factors for breast cancer in Turkey (9, 10). However, factors such as social support and coping style were not assessed in association with stress.

It is accepted that multifactorial etiology and processes, play a role in the development of breast cancer (5). Humans are biological, psychological, and social beings in whom the whole is more than the sum of all parts. The interaction between all these dimensions needs to be considered in the etiology of diseases. Therefore, the effect of factors such as sociodemographic and reproductive characteristics, lifestyle, psychological stress, and coping skills should be integrally considered in the development of breast cancer since all these factors are interrelated with each other. This study aimed to determine the roles of biopsychosocial risk factors in women who are diagnosed as having breast cancer.

Material and Methods

Sample and design

This hospital-based case-control survey study was conducted by the Florence Nightingale Breast Working Group and the Consultation Liaison Psychiatry Department, Istanbul Faculty of Medicine, Istanbul University, Istanbul. The working group included 491 patients who received treatment and follow-up between September 2013 - September 2014 and who accepted to participate in the study. The control group included 512 women who accepted to participate in the study; the control group consisted of women who apply to other departments with no serious disease or cancer.

The majority (61%) of participating subjects (491) were within the age range of 40-59. Among the subjects, the educational level of 39% were university or above. However most of those are housewives (51.9%). Among the study group 69.4% were married. As for the control group, 55.7% of those 512 women were within group of 40-59 years of age, the majority (49.8%) of whom had completed education at a university level or above. The percentage of those working happened to be 58.7%. The majority of the women in the control group were married (76.9%).

Data were collected through semi-structured interviews and the stress assessment form developed by researchers to assess biopsychosocial risk factors related to breast cancer (Figure 1) and the Coping Strategy Indicator developed by Amirkhan. The study was approved by the Department of Ethical Committee, T.C. Bilim University and started after the obtaining consent from the patients.

Measures

The semi-structured interview form included data about participants' social support perceptions, healthy life behavioral patterns (height, weight, physical activity level, smoking, and alcohol consumption), medical histories (having chronic physical illness, family history of cancer), reproductive characteristics (age at menarche, oral contraceptive use, birth, abortus, age at first labor, breastfeeding, menopause), and demographic characteristics (age, education, marital status, employment status, economic condition).

The stress assessment form was categorized into four subdimensions to be able to evaluate patients' stressors and their entire life cycles. This form included data about childhood trauma (being raised in a dysfunctional family, taking responsibilities of adults during childhood, divorced parents, loss of mother/father, a serious health problem, negligence, abuse, being subjected to violence), major life events (death of a loved one, job loss, a chronic serious disease, divorce, economic crisis, earthquake), having a stressor experienced in adulthood but still effective, to understand whether the chronic stress exists (problems with interpersonal relations, conflict, and economic difficulties), and having an important stressor experienced in the last 5 years of the premorbid period that was continuous and caused immense distress (relationship, work stress, economic problems, or unemployment, death of a loved one).

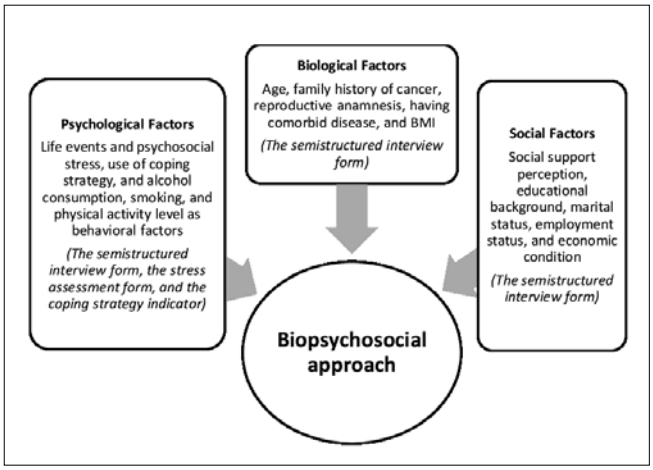

Figure 1. Study design: Biopsychosocial risk factors

The Coping Strategy Indicator was developed by Amirkhan (11), and the validity and reliability analyses of the scale in Turkey were performed by Aysan (12). The Coping Strategy Indicator was selected for (1) practical, (2) theoretical, and (3) psychometric reasons. This measure is a relatively brief coping inventory of 33 items. Ratings are made on a 3-point scale anchored at "not at all" and "a lot." This scale consisted of three subscales: problem solving, seeking social support, and avoidance. The first subscale problem solving methods, the second subscale measured the support received for improving interpersonal relations and relaxation methods, and the last subscale assessed the psychological and physical withdrawal. Higher scores obtained from problem solving and seeking social support subscales indicated the use of positive (effective–active) coping strategies. However, higher scores obtained from the subscale of avoidance meant that the patient used negative (ineffective–inactive) coping strategies.

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (IBM Corp. New York, USA). The body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). The Chi-square test was used in the statistical analyses to evaluate the significant factors associated with breast cancer risk by estimating the odds ratio (OR) and 95% confidence intervals (CI). Logistic regression was used to construct a multivariable model of independent factors associated with breast cancer risk. Forward stepwise regression was used for factor selection, and only factors with a frequency >10% that exhibited univariate significance levels of less than 0.05 were examined. For each factor in the model, the likelihood of breast cancer risk was estimated using the OR and 95% CI. A p value of <.05 was considered significant in the statistical analyses.

Results

The univariate analysis of the biological factors determined that the risk of breast cancer was higher for older women than for women aged ≤39 years (40-59 years; OR, 3.82; 95% CI, 2.75–5.30), (≥60 years; OR, 12.92; 95% CI, 8.07–20.70); for patients with a family history of cancer than for those without (first-degree relative: OR,

2.29; 95% CI, 1.68–3.11; second-degree relative: OR, 1.72; 95% CI, 1.18–2.51); and for patients who experienced early menarche rather than for those whose age at menarche age was ≥14 years (12-13 years: OR, 1.44; 95% CI, 1.09–1.90), (≤11 years: OR, 1.77; 95% CI, 1.06–2.93). It was also higher for patients whose BMI was ≥25 kg/m^2 (OR, 2.32; 95% CI, 1.79–3.02) and for patients who had a chronic disease (OR, 1.85; 95% CI, 1.40–2.46). The study found that oral contraceptive use (OR, 0.72; 95% CI, 0.53–0.96), not giving birth (OR, 0.48; 95% CI, 0.35–0.67), and not breastfeeding (OR, 0.66; 95% CI, 0.49–0.89) were decreasing factors for breast cancer risk. No significant relationship was found between the development of cancer and age at first labor, abortus, and received infertility treatment. All the biological factors were tested using the logistic regression forward-LR analysis. The analysis yielded independent variables that were entered into the model in each step and the data shown in Table 1 in the third step.

According to the univariate analysis of the psychological factors (existence of distress, coping strategy) and behavioral (smoking and alcohol intake, physical activity level) that could be effective in the development of breast cancer, it was found that with the exception of problem-solving coping strategy and smoking, the researched factors were effective. Of these, having a childhood trauma (OR, 1.48; 95% CI, 1.14–1.91), the existence of a major life event (OR, 1.76; 95% CI, 1.22–2.53), chronic stress (OR, 2.01; 95% CI, 1.52–2.67), having a stressor experienced in the last 5 years of the premorbid period (OR, 3.96; 95% CI, 3.02–5.20), use of avoidance (OR, 1.41; 95% CI, 1.07–1.85), seeking social support (OR, 1.53; 95% CI, 1.17–2.01), and low level of physical activity (OR, 1.36; 95% CI, 1.04–1.77) increased the risk of breast cancer, whereas alcohol consumption (OR, 0.51; 95% CI, 0.39–0.67) had a decreased effect on breast cancer risk. All these factors were tested using the logistic regression forward-LR analysis. The analysis yielded independent variables that were entered into the model in each step and the data shown in Table 2 in the fourth step.

The univariate analysis of the social factors that can be effective in the development of breast cancer risk determined the following factors as social factors that increase breast cancer risk: educational background [higher risk for those who graduated from high school (OR, 1.57; 95% CI, 1.17–2.13) or primary school (OR, 2.19; 95% CI, 1.60–2.99) than for those with a bachelor's degree or higher]; marital status, there was a higher risk for those who were [married (OR, 1.65; 95% CI, 1.12–2.42) or widow/divorced (OR, 3.66; 95% CI, 2.23–5.98)] than in those who were single; employment status, a higher risk was observed in those who were unemployed than employed; [retired (OR, 3.05; 95% CI, 2.12–4.39), housewife (OR, 2.94; 95% CI, 2.20–3.92)]; economic condition, there was a higher risk for those who defined their economic condition as moderate (OR, 1.54; 95% CI, 1.17–2.03) or low (OR, 2.99; 95% CI, 1.79–5.01) than as good; and perception of inadequate social support (OR, 2.92; 95% CI, 1.58–3.04). All these factors were tested using logistic regression forward-LR analysis. The analysis yielded independent variables that were entered into the model at each step and the data shown in Table 3 in the fourth step.

In conclusion, when the biological, psychological, and behavioral factors were separately tested using the logistic regression forward-LR analysis, it was found that the breast cancer risk was associated with advanced age, BMI (>25 kg/m^2), family history of cancer, existence of a stressor experienced in the last 5 years of the premorbid period, use of avoidance and seeking social support coping strategies, having a chronic stressor, unemployment, inadequate social support, being widow/divorced, and low economic condition ($p \leq 0.04$). When these biopsychosocial factors were tested using logistic regression forward-LR analysis, independent variables that were obtained that were entered into the model in each step and the data shown in Table 4 in the seventh step.

Discussion and Conclusion

Many factors have an effect on the development of breast cancer**.** These include age, family history of cancer, reproductive factors, lifestyle, and psychosocial factors (13). This study evaluated the biological, psychological, and social factors together and determined that the existence of a stressor experienced in the last 5 years of the premorbid period,

Table 1. Multivariable model: biological factors related to the risk of breast cancer

Variables	B	S.E.	p-value	OR	95% CI for EXP(B) Lower-Upper
Age (years)			<.0001		
≤39 (ref.)				1	
40–59	1.103	.210	<.0001	3.014	1.999-4.544
≥60	1.994	.291	<.0001	7.345	4.152-12.993
The body mass index (kg/m2)					
≤24.99 (ref.)				1	
≥25	.501	.168	.003	1.650	1.188-2.291
Family history of cancer			.004		
No (ref.)				1	
First-degree relative	.606	.197	.002	1.833	1.246-2.695
Second-degree relative	.475	.239	.04	1.608	1.007-2.569

B: Regression coefficient; SE: Standard Error; OR: odds ratio; 95% CI: 95% confidence interval; ref: reference

Table 2. Multivariable model: psychological and behavioral factors related to the risk of breast cancer

Variables	B	S.E.	p-value	OR	95% CI for EXP(B) Lower-Upper
Stressor experienced in the last 5 years					
No (ref.)				1	
Yes	1.495	.171	<.0001	4.459	3.190-6.233
Avoidance coping strategy					
No (ref.)				1	
Yes	.419	.164	.01	1.521	1.103-2.097
Seeking social support coping strategy					
Low (ref.)				1	
High	.390	.163	.01	1.477	1.073-2.034
Chronic stressor					
No (ref.)				1	
Yes	.365	.184	.04	1.441	1.005-2.066

B: Regression coefficient; SE: Standard Error; OR: odds ratio; 95% CI: 95% confidence interval; ref: reference

Table 3. Multivariable model: social factors related to the risk of breast cancer

Variables	B	S.E.	p-value	OR	95% CI for EXP(B) Lower-Upper
Employment status			<.0001		
Working (ref.)				1	
Retired	1.041	.172	<.0001	2.832	2.023-3.965
Housewife	.828	.210	<.0001	2.290	1.516-3.458
Social support perception					
Sufficient (ref.)				1	
Insufficient	.700	.183	<.0001	2.014	1.405-2.885
Marital status			.001		
Single (ref.)				1	
Married	.425	.236	.072	1.529	0.963-2.428
Widowed/Divorced	1.108	.297	<.0001	3.027	1.691-5.421
Economic condition					
Good (ref.)				1	
Moderate	.364	.293	.214	1.438	0.810-2.557
Low	.699	.309	.02	2.012	1.096-3.690

B: Regression coefficient; SE: Standard Error; OR: odds ratio; 95% CI: 95% confidence interval; ref: reference

perception of inadequate social support, use of avoidance and seeking social support coping strategies, being a housewife, family history of cancer, advanced age, and BMI ≥25 kg/m^2 increased the risk of breast cancer.

Age (13) and family history of breast and/or ovarian cancers (13, 14) are the most known risk factors for breast cancer. In line with these studies, present study implied that having a first-degree relative with breast cancer and being more than 40 years distinctly increased risk. The other most frequently researched risk factors are reproduction and obstetric history variables. Various studies have found that there exists a relationship between early menarche (10, 13), advanced maternal age (10, 13), and breast cancer. The protective role of breastfeeding in breast cancer is also included in the literature (2, 15). Iqbal et al. (16) demonstrated no correlation between breast cancer risk and labor, age at first labor, and breastfeeding. The present study also found no differ-

Table 4. Multivariable model: biopsychosocial factors related to the risk of breast cancer

Variables	B	S.E.	p-value	OR	95% CI for EXP(B) Lower-Upper
The stressor experienced in the last 5 years					
No (ref.)				1	
Yes	1.734	.208	<.0001	5.662	3.767-8.511
Age (years)			<.0001		
≤39 (ref.)				1	
40–59	1.229	.251	<.0001	3.416	2.090-5.585
≥60	2.487	.401	<.0001	12.024	5.482-26.375
Social support perception					
Sufficient (ref.)				1	
Insufficient	.773	.234	.001	2.166	1.371-3.424
Avoidance coping strategy					
No (ref.)				1	
Yes	.632	.200	.002	1.882	1.271-2.785
Employment status			.002		
Working (ref.)				1	
Housewife	.688	.227	.002	1.989	1.275-3.103
Family history of cancer			.006		
No (ref.)				1	
First-degree relative	.660	.241	.006	1.934	1.207-3.101
The body mass index (kg/m2)					
≤24.99 (ref.)				1	
≥25	.444	.206	.03	1.559	1.042-2.333

B: regression coefficient; SE: standard error; OR: odds ratio; 95% CI: 95% confidence interval; ref: reference

ence between the controls and the study group in terms of age at first labor, and high level of labor, and breastfeeding experience in patients with breast cancer; this might be because the control group comprised of young and single women. Various studies that researched the relationship between breast cancer and abortus (15), and the use of oral contraceptives (10, 14, 15) reported that these factors could increase breast cancer risk. The multivariable analysis of the present study did not determine factors related to reproduction and obstetric history as independent risk factors. Contradictory results might be obtained because reproductive factors are influenced by certain variables such as demographics, culture, and subtype of breast neoplasm. Presence of chronic diseases such as diabetes and hypertension was also found to be a risk factor for breast cancer (2, 10); the findings of the present study are consistent with the published reports. The effect of obesity on breast cancer was examined with diet or BMI, and similar to the results of the present study, many studies (5, 16) found a relationship between BMI ≥25 kg/m^2 and risk increase in the development of breast cancer**.** When the biological factors were assessed separately or along with the biopsychosocial factors, it was seen that advanced age, obesity, and a family history of cancer were independent and significant risk factors in the development of breast cancer.

It is a common belief in society that stress is a risk factor for cancer, especially for breast cancer. Various studies that explored the effect of psychological factors on the development of breast cancer have been published in the literature. Important variables such as the number and type of adverse life events and the time of exposure to stress and methodologic differences led to contradictory findings (4). Consequently, the stress assessment form was developed to assess an individual's childhood period, source of major and chronic stressors in adulthood, and important stressors experienced in the last 5 years. The univariate analysis found that a trauma experienced during childhood was associated with breast cancer; other studies also reported similar findings (17). Ginzburg et al. (18) determined similar childhood experiences of the participants in the study and control groups. The present study also found that a trauma experienced during childhood was not an independent risk factor in the multivariate analysis. Three meta-analyses that assessed the relationship between breast cancer and stress between 1966 and 2007 presented inconsistent results and suggested the lack of evidence remarking the diversity of research designs; however, it was stated that the correlation between breast cancer risk and stressful life events could not be ignored (19, 20, 21)**.** Although the univariate analysis performed on the present study determined major life events, chronic stress, and having a stressor experienced in the last 5 years as risk factors, the logistic regression analysis of the psychological variables did not find major life events as an independent risk factor. Having a stressor experienced in the last 5 years

among the biopsychosocial variables was determined as an independent variable that considerably increased the risk of breast cancer. A study conducted in Turkey by Ceber et al. (9) found no difference between the study and control groups in terms of the degree of stressor experienced in the last 5 years. On the other hand, similar to the results of the present study, it was reported that the self-reported stress in the last 5 years (15, 22, 23), having a stressful vital event in the last 2 years (24), and having stressful life events before the diagnosis (25) were associated with breast cancer.

The effect of stressful life events was related with the type and time of the event, and with how it was coped. This study determined that inadequate social support, use of avoidance and, seeking social support methods increased breast cancer risk. The possible benefits of effective stress coping strategy and of social support on health care, life quality, and immunity are well known (7, 26). Studies conducted on women with breast cancer and the effect of social support and coping strategies focused on the period after cancer diagnosis and reported that these played a role in decreasing distress, and adaptation to the disease (26). A limited number of studies are available about the effect of coping styles and social support on the development of breast cancer; both studies were conducted many years ago, and this issue was not adequately researched. Edwards et al. (27) reported that the correlation between breast cancer and life events was not moderated by coping or availability of social support. Geyer (6) proposed social support as modifying the effect of stressful life events. Chen et al. (25) reported a significant increase in breast cancer risk for women experiencing a severely threatening life event and confronting stress by focusing on the problem at hand. However, it was stated that this interaction was not clear and hence should be tested using a multivariate model. Price et al. (7) concluded that stress did not cause breast cancer in women, but the absence of intimate emotional support could increase the vulnerability to this disease. Ollonen et al. (28) reported a moderate level of relationship between the increasing breast cancer risk and defense mechanisms, and inadequate coping. The study explained the biological effect of defense and coping strategies on cancer; these can directly affect hormonal, immune, and nervous system functions, or indirectly through behaviors such as alcohol intake, smoking, nutrition, and physical activity. The multivariate analysis in our study assessing the stated behaviors did not determine these behaviors as important risk factors. The present study results showed that perception of inadequate social support and use of avoidance coping mechanism were independent variables related to breast cancer. Further studies are required to elucidate the underling mechanisms of these factors.

The incidence of breast cancer varies with developmental level of the country and ethnicity. Economic condition, educational background, employment status, and marital status are important sociocultural variables. The univariate analysis of this study determined a significant relationship between breast cancer and these factors, and the regression model found that housewives had a higher risk of breast cancer. A study conducted in Pakistan by Anjum et al. revealed similar results (29). Othieno-Abinya et al. (14) conducted a study in Kenya; the regression analysis of the study determined that breast cancer was less prevalent in housewives and unemployed women, with no difference in terms of education and marital status. Conflicting conclusions are reported in the literature. It appears that the risk posed by becoming a housewife for developing breast cancer is coincidental. Taking this into consideration, it would be appropriate for this matter to be researched using a different methodology. The studies comparing the effect of social and economic status on the outcome focused mainly on the level of education and income. It was found in the literature that women who had higher education and income at the individual and social levels had a higher risk of breast cancer (15, 30). Some studies examined the relationship between work stress and breast cancer, but no difference was found (31). Furthermore, unemployed women had lower education and income level, and it was associated with the absence of socioeconomic support.

Breast cancer is a disease that has a multifactorial etiology and these factors interact with each other. Biopsychosocial aspects are becoming a greater part of many different healthcare systems. The present study showed a relationship between breast cancer risk and manageable variables (obesity, stressor and coping strategy, social support, and employment status), age and family history of cancer, which are biopsychosocial factors. It was also found that having a stressor experienced in the last 5 years was an independent and significant risk factor. Assessing factors such as coping and social support together, which can change the effect of stressful life events, is important while researching the effect of stress. Conducting large-scale case-control prospective studies and researching the effect of stress using biological parameters will be helpful in the future.

The present study had certain limitations. Firstly, this was a retrospective study. Women's lifestyles can change before and after cancer diagnosis; therefore, it can be harder to objectively assess life events. Secondly, this study used self-report surveys, and the sample group did not reflect all Turkish women. Despite the aforementioned limitations, the strength of this study was that it evaluated many biopsychosocial factors together.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bilim University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Case Report

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Bilateral Breast Cancer with Neurofibromatosis Type 1 Patient: Case Report

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ABSTRACT

Neurofibromatosis type 1 (NF1) is autosomal dominant and it is the most common hereditary disease. This case report is about a woman and her daughter. Both of them are NF1 and mother also has metachronous bilateral breast carcinoma. We analyzed expressions of 84 genes related with DNA Repair by Real Time PCR (AB Applied Biosystem 7000 Sequence Detection System;

Thermo Fisher, Foster City, CA, USA). We also performed NF1 sequencing analyzing in exon 9 of the NF1 gene for mother. In Real Time PCR analysis of DNA Repair Genes, expression chances were predominant both in mother and daughter compared with control group. When the mother and daughter's expression profiles were compared, similar DNA repair array gene expression profiles were observed and the expression of DDB2, MGMT, MLH1, POLB UNG, XPA genes were high in both mother and daughter.

In sequencing analysis, we obtained a mutation in c.1246 C>T. This mutation is reported to be common in NF1 cases with breast carcinoma. Our results indicate that the daughter with NF1 is probably prone to have malignancy in her future life. She should be carefully followed up for early diagnosis of a probable malignancy.

Keywords: Neurofibromatosis type 1, breast cancer, bilateral

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Introduction

Neurofibromatosis type 1 (NF1) is autosomal dominant and it is most common hereditary disease**.** It is considered to be one of the tumor predisposition syndromes (1). Neurofibromin is a protein coded by NF1 gene located at 17q11.2 (2). It is involved in proliferation by affecting intracellular signaling pathways; by hydrolysis of active Ras-GTP, it causes activation of Ras, MAPK, PI3K and mTOR pathways causing proliferation (3).

Not all but some of NF1 patients develop tumors during their life. Neurofibromas, optic gliomas, hamartomas are benign lesions. Loss of heterozygosity in NF1 gene might predispose NF1 patients to certain malignancies such as malignant peripheral nerve sheet tumor, rhabdomyosarcoma, pheochomocytoma, breast cancer, gastrointestinal stromal tumor, neuroectodermal tumors. Additional genetic alterations might be required for their development. In all of NF1 patients with malignancies genetic testing must be performed to understand the mechanism and reason of malignancy association.

Breast carcinoma in NF1 patients was first reported by Borberg et al. (4). Murayama reported 34 NF1 patients with 38 breast cancers (5). Breast cancer among NF1 patients with malignancy is reported about 10-15%, and 18.5% of them occur before the age of 30.

In this paper we aimed to report a mother with bilateral breast cancer and her daughter with NF1 that DNA repair gene expressions and NF1 mutation were analyzed.

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Case Presentation

Patient: In this study, we report of a case of NF1 patient, 44 years old, female. Metachronous bilateral breast carcinoma was observed during follow up. She was diagnosed NF1 at age of 26, she has multiple café au lait spots, neurofibromas and her father also has NF1 disease. She underwent operation left breast excision with axillary dissection because of intraductal carcinoma (comedocarcinoma) and fibrocystic disease in 1996. At that time, there was no lymph node involvement. She was followed up by breast ultrasonography and mammography. Mammography showed BIRADS three lesion in right breast at 2007. In 2009, right breast was observed as BIRADS four. In 2012, right breast mammography showed BIRADS 5 and right breast biopsy demonstrated an invasive ductal carcinoma (modified Bloom Richardson in two upper inner quadrants and diffuse intraductal carcinoma (comedo, cribriform, micropapillary) and tumor was positive in two lymph nodes. She underwent modified radical mastectomy and axillary dissection operation to right side. Chemotherapy and radiotherapy were applied. She is now alive on follow up with no recurrence in two years.

Daughter: She has a daughter, 8 years old, with NF1 diagnosis. She has café au lait spots and freckles. She does not have any neurofibromas or any other tumors. She was diagnosed with NF1 when she was 18 months old.

Informed consent was obtained from patients. Peripheral blood was obtained from each case. Mononuclear cells were separated using the Ficoll-Paque density gradient method. DNA (Roche; Mannheim, Germany) and RNA isolation (Macherey Nagel; Düren, Germany) were carried out. After RNA isolation (Macherey Nagel; Düren, Germany) and cDNA converting (NY-X Technic ATC 401 model, San Diego, CA, USA), expressions of 84 genes related with DNA Repair in standard array (Qiagen; SABiosciences PAHS 042, United Kingdom) were determined by Real-Time PCR (AB Applied Biosystem 7000 Sequence Detection System; Thermo Fisher, Foster City, CA, USA) both for mother and daughter. Fold changes comparing with control group (8 cases without any diseases) and comparing with NF1 patient without malignancy were evaluated. On the other hand; for sequence analysis, after DNA isolation, PCR and PCR clean up were carried out, respectively. Later SAP/EXO (Thermo Fisher; Paisley, UK) was carried out and then was passed to the next step which included Big Dye (Thermo Fisher; Paisley, UK) and Big Dye Clean Up. After Big Dye Clean Up, the sequencing for NF1 gene was carried out.

We performed NF1 sequencing and observed that there is a mutation in c.1246 C>T in exon 9 of NF1 gene.

DNA repair array gene expression results showed that when this patient's results compare with the other NF1 patients without malignancy; ATR, CCNO, MLH1, NEIL1, NTHL1, RAD18, RAD 51, XRCC1, XRCC3 genes are overexpressed and ATM, BRCA1, BRCA2, ERCC4, EXO1, FEN1, LIG1, LIG3, MPG, MRE11A, MSH2, NEIL2, PMS1, POLD3, RFC1, SMUG1, TDG, TOP3B genes are down-regulated in this patient (mother).

PNKP, RAD18, XAB2, XRCC3, XRCC4 and XRCC5 genes were down-regulated compared with control group in her daughter. RAD18 was the most down-regulated gene. The daughter has similar DNA repair array gene expression profile with the mother. This might be a clue that she might have malignancy in her future life. BRCA1, BRCA2, DDB2, MGMT, MLH1, POLB UNG, XPA genes might be possible clue for developing breast cancer.

When malign tumor cases compared which are NF1 and without NF1, we observed that DDB2, MGMT, MLH1, POLB UNG, XPA genes were upregulated for each group to control group. This fold change was more than 10 times.

ERCC1(p: 0.015) and TREX1(p: 0.026) genes were down-regulated when the patient's results compared with the child and they were statistical significance in these 84 genes (Mann-Whitney U Test).

- TREX1: dauhter: 0.142 ± 0.108 (0.078-0.346)
- TREX1: mother: 0.062±0.026 (0.015-0.090)
- TREX1: dauhter: 0.069±0.065 (0.020-0.197)
- TREX1: mother: 0.021±0.006 (0.016-0.032)

Discussion and Conclusion

In this paper, we reported a mother and her daughter case with NF1 diagnosis. The mother suffered from bilateral metachronous breast cancer. DNA repair gene expressions were evaluated for both. The daughter has similar DNA repair array gene expression profile with the mother which was thought to be a clue that she might have malignancy in her future life.

Patil and Chamberlain reviewed the literature for neoplasm associated with germline and somatic NF1 gene mutations (6). Treatment is the same with sporadic breast cancer cases.

Malignancies in NF1 patients are reported to occur at an earlier age than their sporadic counterparts and they have poorer prognosis.

There are more than 500 different NF1 mutations, besides mucinous carcinoma, ductal carcinoma in situ, and squamous cell carcinoma has both invasive ductal carcinoma or lobular carcinoma of breast might be observed in NF1 cases also been reported. In our case the previously observed left breast cancer was intraductal carcinoma and the other breast showed invasive ductal carcinoma 9 years later. The additional genetic alterations in NF1 patients with breast cancer have not been defined yet.

BRCA1 mutation has been demonstrated in some of NF1 associated breast cancer cases. In this study we found that there was a mutation in NF1 gene, c.1246 C>T in exon 9 and BRCA1 and BRCA2 gene expressions were down-regulated. This mutation in NF1 is already available in the literature (7). The altered expression evident in the present mother case might show us that this kind of alterations in combination with a mutation c.1246 C>T might lead to breast cancer.

The other point is that the increase observed in expression of DNA repair genes. Our results point to a shift in the phenotype towards. The DNA repair genes expression had not been studied in any NF1 patients before in the available English-language literature.

In conclusion; we here report a mother and her daughter who both have NF1. The mother had bilateral metachronous breast cancer and NF1 c.1246 C>T mutation. DNA repair gene expressions were similar in mother and daughter. By this reason, we think that the daughter might also have breast cancer in her future life. The DNA repair gene expression decrease or loss might be predictor for cancer susceptibility in NF1 patients. We conclude that NF1 patients might be screened for DNA repair gene expression status to guess possible malignancy.

Informed Consent: Written informed consent was obtained from patients in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - D.D., S.A.; Design - D.D., S.A.; Supervision - D.D., N.O.; Resources - D.D., Z.A.; Materials - D.D., S.A.; Data Collection and/or Processing - D.D., S.A., N.O.; Analysis and/or Interpretation - D.D., S.A., N.O.; Literature Search - D.D., Z.A.; Writing Manuscript - D.D., S.A.; Critical Review - D.D., S.A.

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Case Report

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An Unusual Gastrointestinal Stromal Tumor Presentain: Breast, Liver and Lymph Node Metastasis

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ABSTRACT

Gastrointestinal Stromal Tumors (GIST) are the common mesenchymal tumors of gastrointestinal tract. They can display benign and malignant clinical behavior. The most common metastasis sites of malignant stromal tumor are liver, peritoneum, lung and bones. Metastasis to breast is extremely rare. Here, we present a case of GIST with liver, bone, lymph node and breast metastasis by reviewing the literature.

Keywords: Gastrointestinal stromal tumor, metastasis, breast, lymph node

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Introduction

Stromal tumors are the prominent mesenchymal tumors of gastrointestinal tract (GIT) (1). They are more apparent in upper middle age, mostly in 5th and 6th decades. They occur equally in both sexes (1). Gastrointestinal Stromal Tumors (GISTs) are most commonly localized in the stomach (40-70%) and may be found in the intestine (20-32%), colon (10%) and esophagus (5%) (1, 2). They also can be seen in extra-GIT sites like mesentery, omentum and retroperitoneum (2). Major patient complaints regarding GISTs are upper abdominal pain, GIT bleeding and abdominal masses (1). Interstitial cells of Cajal (ICC), which GISTs are thought to originate from, both express tyrosine kinase receptors (c-kit) and stain with CD34 and Vimentin. KIT (CD117) is a transmembrane tyrosine kinase receptor, which is expressed in hematopoietic stem cells, germ cells, mast cells, melanocytes and ICC (2). C-Kit positivity is an important parameter in diagnosis of GIST. Recently, a specific marker, namely discovered on GIST1 (DOG-1), has been discovered for GIST diagnosis. It is shown to be positive on ICCs and gastric surface epithelium. DOG-1 is also expressed in high amounts in KIT mutation-negative cases besides typical GIST cases (3). Immunohistochemical diagnosis of GIST is adopted when mesenchymal tumors stain positive with c-Kit (CD117) and the DOG-1 where the rest of mesenchymal cell markers were negative. Demonstration of CD117 and recently DOG-1 positivity immunochemically stands for the standard technique of definitive diagnosis of GIST. CD34 is positive in 70-80% of the cases. Vimentin is diffuse and strong positive in many stromal tumors. SMA is positive in 30-40% and S100 in 5% of GISTs. Staining with desmin is rare (1). Malignant stromal tumors mostly metastasize to liver, peritoneum, lungs and bones (4). Brain and lymph node metastases are unusual (4). No breast metastasis was presented in literature before.

Hereby, we present a case of GIST with liver, bone, lymph node and breast metastases and aimed to discuss its unusual metastatic reviewing literature.

Case Presentation

A 46 year-old woman was referred to us from another health facility with the complaint of back pain. The radiological imaging studies revealed multiple liver metastases with the largest being 5.5 cm in diameter as well as multiple bone involvements. Positron Emission

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Computed Tomography (PET-CT, General Electric Medical System, Milwaukee, USA) demonstrated elevated F-18-fluoro-2-deoxyglucose (FDG) uptake in her left breast in addition to the above-mentioned lesions. Histologic samples taken from abdominal lymph nodes and liver revealed neoplastic lesions composed of cells with prominent hyperchromatic nuclei and spindle-shaped cytoplasm. Immunohistochemistry studies showed strong positive staining with CD117 (Code A4502, Dako, California) in Figure 1 and DOG-1 (Clone SP31, Thermo Scientific, USA) in Figure 2, positive staining with Vimentin (Code-Nr. M 0725, Dako, Denmark) and negative staining with CD34 (Clone QBEnd-10, Dako, Denmark), S100 (Code ZO311, Dako, Denmark) and Desmin (Clone D33, Dako, Denmark) in both liver and lymph node tissues. The patient was diagnosed to have GIST metastasis and therefore was started on imatinib therapy. A control PET-CT obtained on the second month of imatinib treatment demonstrated progression in liver metastases, variable response in bone metastases and partial regression in breast and lymph node metastases. No mass was observed on the physical examination of either of the breasts and the axillae. Breast ultrasound and Magnetic Resonance Imaging showed two small lesions of 5 and 3 mm in close location, which both were thought to be benign.

As for the fact that nuclear regression had been experienced in the left breast under imatinib therapy, tissue diagnosis was planned to rule out malignancy. After the suspected area was marked with needle localization by ultrasound, a wide excisional biopsy was performed. When the specimen of 10x4x4 cm yellow color fatty tissue was examined macroscopically in serial sections, no significant mass was observed in cross-sectional surfaces. Complete sampling of the specimen demonstrated fibroadipose and acinar tissue, as well as two lesions in 3x2 mm and 2x2 mm size composed of spindle cells with prominent nuclei and spindle-shaped cytoplasm (Figure 3). These cells stained strongly with CD117 (Figure 4) and DOG1 (Figure 5) and did not stain with S100, CD34 and SMA (Clone 1A4, Code M0851, Dako, Denmark) immunohistochemically. Microscopy in 10x High Power Magnification (HPM) of these lesions showed 4-5 mitoses. Ki67 (Clone MIB-1, Coce M7240, Dako, Denmark) proliferation index was calculated as 3-4%. The case was interpreted as a GIST metastasizing to liver, lymph nodes, bones and breast when evaluated immunohistochemically with its histomorphological findings.

A lumbar MRI scan was obtained due to increased bone pain, which revealed progressive bone metastases. The imatinib dose was doubled; however, she was lost to follow-up. Patient gave orally informed consent.

Discussion and Conclusion

Gastrointestinal stromal tumors (GISTs) can occur anywhere along

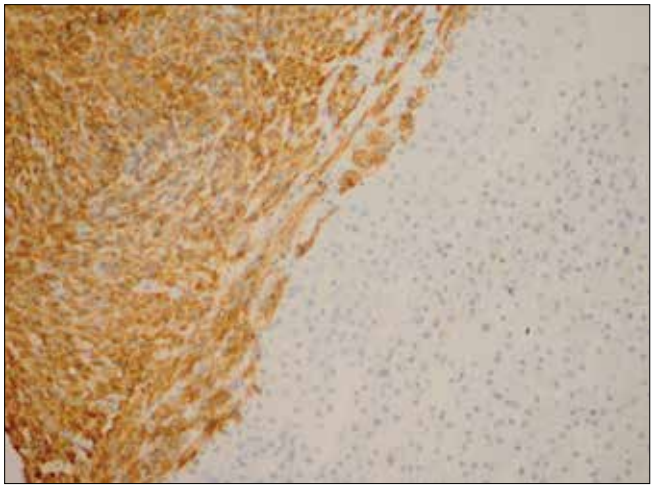

Figure 1. CD117 positivity by immunohistochemistry in liver

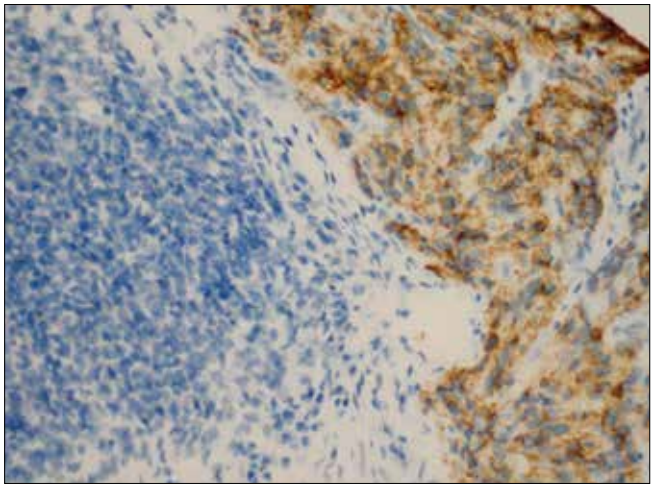

Figure 2. DOG 1 negative in lymphoid cells in lymph node, while positive in infiltration areas

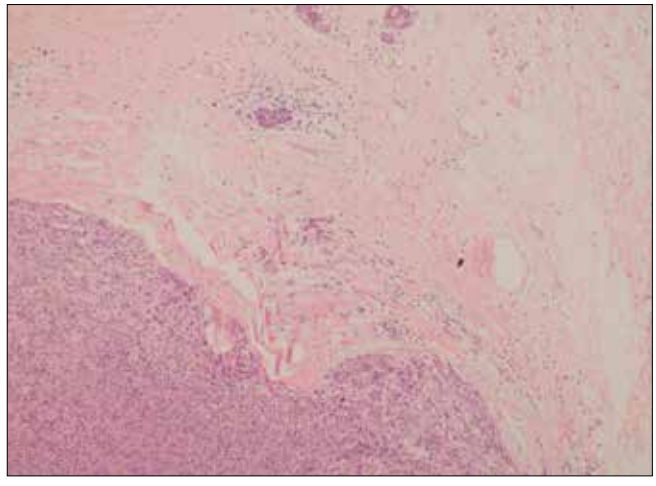

Figure 3. Tumor infiltration well separated from mammary stroma, as well as ductal structures
(H&E stain, x100)

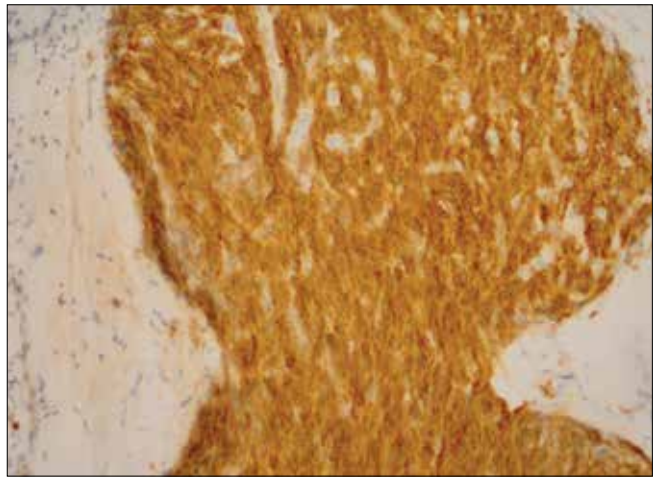

Figure 4. CD117-positive tumor areas in breast

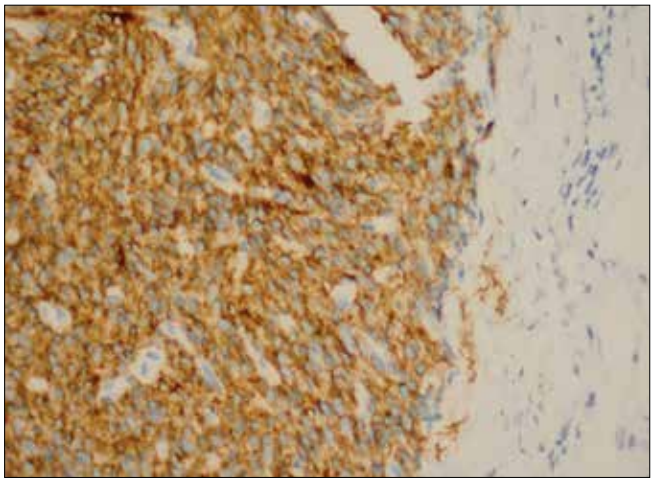

Figure 5. DOG1-positive tumor areas in breast

the Gastrointestinal tract (GIT) from esophagus to anus besides in omentum, mesentery, retroperitoneum deriving from Interstitial cells of cajal (ICCs) (3, 5). C-kit and DOG-1 positivity in used in the pathologic diagnosis of GISTs (3). Stromal tumors like leiomyomas, leiomyosarcomas, desmoid tumors, mesenteric fibromatosis and fibrosarcomas are considered in differential diagnosis. Tumor size, number of mitosis and localization are the most important prognostic factors of GISTs (1). GISTs are structured as spindle-like in 70%, epithelioid in 20% and mixed in 10%. Spacing signet-ring-like areas can also be observed. Major route of metastases of malignant stromal tumors are liver, peritoneum, lungs and bones (4). Brain and lymph node metastases are extraordinary (4). No breast metastasis of GIST was declared before. There are cases in the literature presenting invasive breast cancer of the breast accompanying GIST as a second primary tumor (6, 7). Subash et al. (6) presented a case with GIST in which Position Emission Computed Tomography (PET-CT) demonstrated an increased uptake in her left breast and breast biopsy proved an invasive ductal breast cancer . Obinna et al. (4) presented a case with GIST who developed an intramammary lymph node metastasis and intestinal metastasis . Our case presentation seems to be the first in literature to demonstrate a breast metastasis of GIST. CD117 is expressed in Phyllodes tumors (PT) of breast (8). This study showed weak staining with CD117 in 5 of 17 PTs (8).

Gastrointestinal stromal tumors rarely can contain signet-ring-like components. Epithelioid type GISTs comprising signet-ring-like cells must be differentiated from invasive lobular cancers of breast in terms of diagnosis. In the study of Yared et al. (9) CD117 was applied to the tissue samples obtained from 21 normal breast epithelia, 24 benign breast lesions, 29 in situ breast carcinomas and 41 invasive carcinomas. Positive staining was demonstrated in 100% of normal breast epithelia, 88% of benign breast lesions, 20% of in situ carcinomas and 18% of invasive breast carcinomas. Of the 6 invasive breast cancers which stained strong positive, two were lobular, one was ductal and one was signet ring cell cancers . Also, CD117 positivity was shown in a case of gastric epithelioid GIST presented in the literature, which later presented an axillary mass and ER and GCDFP- 15 positivity in breast and gastric samples resulting in the diagnosis of primary lobular carcinoma of the breast and a gastric metastasis (10).

Therefore, especially before diagnosing epithelioid-type stromal tumors, lobular and signet ring cell carcinomas of the breast must be differentiated by immunohistochemical and radiological examinations. Studies concerning GIST in the literature commonly present liver, lung and bone metastases. Hereby, we presented the first case of GIST metastasizing to breast, which we think is a very extraordinary condition and discussed according to the literature. It must be kept in mind that demonstration of a spindle cell neoplasia can either belong to a primary tumor or a metastasis. Therefore, CD117, which is stained both in GIST and most spindle cell bearing conditions of the breast such as Phyllodes tumors, and DOG1 staining studies must be added to foresee GIST metastasis.

Informed Consent: İnformed consent was obtained from patient who participated in this study.

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Letter to the Editor

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The Spectrum Theory in Breast Cancer Is Controversial

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Dear Editor,

I have read the article titled "Paradigm Shift from Halstedian Radical Mastectomy to Personalized Medicine" with a great interest (1). Meanwhile, I felt to emphasize that following points should be taken into consideration;

1-As everyone knows, the systemic treatment paradigm of breast cancer pathobiology suggested by Bernard Fisher and his team has been obtained from thorough and cumbersome studies (by both experimental and randomized clinical trials) taking nearly 15 years. The theory of Halsted based on Virchow hypothesis is also represents a long and detailed clinical and laboratory experience. The third theory named "Spectrum Theory" has been completely rejected by Fisher in 2010. Finally, 15 years have passed, and, it has not accepted as a new paradigm for management of breast cancer (2).

Therefore, the sentence in the paper expressing as "Today, we accept that the intermediate paradigm as a combination of Halstedian and Fisherian hypothesis" is controversial.

2-Moving from Fisher paradigm, primary chemotherapy (PCT) has gained a wide application in the treatment of locally advanced breast cancer. A significant disease-free and overall survival advantage has been shown in randomised trial (NSABP B-18 and B-27) in cases with complete pathologic response to PCT) (3).

3-Novel techniques of breast reconstruction like autologue fat grafting and autologue free dermal fat grafting should be considered as new and modern alternatives in tayloring the oncoplastic surgery (4-5).

4-Although its use limited to small and unifocal tumors, intraoperative radiotherapy (IORT) is an inexpensive and reliable alternative in tayloring of radiotherapy (6).

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