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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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Instructions to Authors

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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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Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Materials, Results, Discussion and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

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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Images in Clinical Practices: Our journal accepts original high quality images related to the cases that we come across during clinical practices, that cite the importance or infrequency of the topic, make the visual quality stand out and present important information that should be shared in academic platforms. Titles of the images should not exceed 10 words. Images can be signed by no more than 3 authors. Figure legends are limited to 200 words and the number of figures is limited to 3. Video submissions will not be considered.

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.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

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)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

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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.

Journal Article: Little FB, Koufman JA, Kohut RI, Marshall RB. Effect of gastric acid on the pathogenesis of subglottic stenosis. Ann Otol Rhinol Laryngol 1985; 94:516-519. (PMID: 4051410)

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

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Contents

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The Big Data Revolution for Breast Cancer Patients

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The origins of Big Data date back to 1941, when the first references were made to the notion of "information explosion" in the Oxford Dictionary of English. James Maar has highlighted in 1996 in a report of the National Academy of Sciences the concept of "massive data set" (1). But it was only in 1997 that the precise term 'Big Data' first appeared in an article in the Digital Library of the Association for Computing Machinery (2), referring to the technical challenge of analyzing large sets of data. It has since been used to designate "structured or unstructured data, whose very large volume requires adapted analysis tools". Web giants (Google, Amazon, Facebook, Apple, Twitter) have developed such tools over the past decade, ensuring a constant marginal cost of data exploitation, regardless of volume.

Today, Big Data is characterized by 5V: Volume, Velocity, Variety, Veracity and Value of the data exploited. The drop in storage prices and the increase in computing capacity are at the origin of the large volumes and the high speed of data processing. The variety of data (images, texts, databases, connected devices, etc.) is mainly due to the increasing digitization of information media. Finally, the truth of the data, from which the value of the work is derived, is a central issue for any project of automated data analysis. Indeed, an algorithm is really powerful if the data are numerous, exact, and well-adapted to the question to be solved. Multiplying sources and crossings without worrying about the quality of the data can only lead to erroneous results, notably in the domain of health. The development of Big Data has been accompanied by the emergence of "Open Data" which correspond to data generated and maintained by various organizations and made available to citizens and businesses.

The 5 V, however, are insufficient to characterize the essence of the innovation brought by Big Data. The mastery of these algorithms is at the heart of the business of data scientists.

The diagnosis and treatment of breast cancer have rapidly evolved during the past three decades. Part of this evolution is due to individual or organized breast screening programs and progress of breast imaging technics. Indeed, a sub-domain of artificial intelligence called "machine learning" makes it possible to build algorithms able to accumulate knowledge and intelligence from experiments, without being human-guided during their learning, nor explicitly programmed to manage a particular task, hence their central role in the data value chain while the rest is due to the evolution of surgical techniques or medical treatments. Recently, the advent of Big Data technologies has generated a lot of interest among the medical community concerned with breast health. Indeed, the available storage capacities increased exponentially during the last three decades, thus leading to bigger volumes and variety of stored medical data (mammography scans, 3D ultrasound, MRI, genomic data, pathological data…). Until now, these data were generally exploited at an individual level during a specific period of time in order to establish a diagnosis, a therapeutic protocol, to follow the disease evolution and to estimate a prognosis for a specific patient. Moreover, only structured data, which represented a small fraction of accessible and interesting information sources, were exploited on a statistical scale. The rest was stored in data graveyards that the medical staff barely sees. The big promise of Big Data is to allow the exploitation of all data sources, including unstructured ones such as textual patients reports or images, thus influencing medical research, and ultimately patient care.

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To understand more precisely how Big Data may revolutionize breast health care, it is necessary to consider two progresses. Firstly, the software landscape that emerged in the past decade allows the implementation of predefined operations on huge volumes and different varieties of data. Secondly, machine learning algorithms and their practical implementations in programming languages, can learn from data in order to extract patterns and correlations, and ultimately produce valuable insights. The so-called data scientists are the experts in juggling these sets of techniques.

Various medical projects based on Big Data techniques were launched in the past few years in the domain of breast health, with many implications on the understanding of prognosis and on decision making (3, 4). One of these ongoing clinical trials (ClinicalTrials.gov Identifier: NCT02810093) consists in analysing textual records of patients suffering from breast cancer. The analysis is performed using machine learning algorithms that extract and structure a wide variety of information, including medical history, risk factors, size of tumours, lymph node involvement, presence of specific biomarkers, use of different treatments or patients' evolution. Once this information is structured, a second iteration of statistical modelling is performed, with many interesting insights on specific subpopulations, the importance of certain biomarkers for prognosis, or the adequacy of the decision criteria used by the medical staff in breast cancer treatment. Their results will probably enhance our understanding of the many intricate mechanisms underlying cancer development, or therapeutic resistance.

These achievements highlight the considerable potential of Big Data techniques in breast cancer care, but also for other pathologies. Consequently, medical time is progressively changing: whilst up to 30 years were necessary to gather data using cohorts to answer a specific question, such as the impact dietary factors, physical activities, alcohol consumption, night work on breast cancer development, Big Data technologies now allow us to analyse all sorts of existing data to isolate the relevant information for answering these numerous medical questions. More generally, the medical research paradigm is slowly shifting from the logic of hypothesis verification on ad hoc constructed populations, to the discovery of interesting correlations after the data collection phase.

Transdisciplinarity is central to the success of these innovative studies. Learning a semantics that is shared between the medical staff and data scientists takes time, and the breast disease units' experience in transversal organizations will be very helpful in defining a frame for these collaborations. In addition to the medical staff and data scientists, Big Data projects should involve patients, and more generally civil society, since only a strict compliance with privacy rules can ensure their success and viability.

Moreover, a truly international vision of the future of breast cancer care is necessary, and more generally of how data exploitation can be at the service of public health policies, while the time frame to develop these projects may be very quick, the huge amount of data being available today. Junior doctors should get involved early in their training in the Big Data research thematic. Indeed, in a very near future, it will be up to them to define the interesting questions that need to be answered, the data sources where to look for answers, the data that need to be collected, and the ethical frames for Big Data projects. More generally, all the medical staff needs to progressively learn how to incorporate the new possibilities offered by the Big Data revolution to the day-to-day practice with patients.

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Editorial Letter

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Predicting Lymph Node Metastasis in the Era of Z0011- Necessity and Methods Remain in Question

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The article, previously published in the European Journal of Breast Health with a title of "Factors Influencing Non-sentinel Node Metastasis in Patients with Macrometastatic Sentinel Lymph Node Involvement and Validation of the Three Commonly Used Nomograms" addresses a now commonly debated topic of how to address the axilla in the setting of macrometastatic disease (1). The findings of ACOSOG Z0011 have been practice changing throughout the world (2-4). With that landmark study stating that patients with 2 or fewer clinically occult, metastatic sentinel lymph nodes (SLN) experience the same overall and disease free survival with adjuvant radiation and systemic therapy alone after breast conserving surgery as do patients who proceed with axillary lymph node dissection after sentinel node biopsy (5). However, the question remains, "How do we manage those with 3 or greater positive sentinel nodes?" The authors note that, on multivariable analysis, pathologic tumor size >2cm, higher ratio of metastatic SLN to total dissected SLN, metastatic tumor size >1cm and extracapsular extension were associated with a statistically significant likelihood of metastatic disease in the non-sentinel nodes. Only one of the studied nomograms correctly predicted results in this dataset. These are interesting findings and do help clinicians to risk stratify, although most would still proceed with dissection in the absence of large prospective data. Of course, the authors of Z0011 never stated that those with 2 or fewer positive SLN were unlikely to have residual disease in the axilla. They instead stated that whatever disease remained was adequately treated by adjuvant therapy in lieu of additional surgery. Studies like this article are the next step towards trials that can answer that question for patients with greater than 2 positive SLN. It suggests that perhaps criteria other than simply number of lymph nodes involved can be predictive of residual disease. The much more meaningful question that this study helps us begin to ask is "are there factors other than positive SLN count that can predict outcome if axillary dissection is omitted?" Should this question be answered by way of clinical trial or other high level evidence, we will truly find ourselves personalizing therapy for patients with breast cancer with macrometastatic disease to the axillary lymph nodes.

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Review

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Breast Cancer Prevention: Current Approaches and Future Directions

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ABSTRACT

The topic of breast cancer prevention is very broad. All aspects of the topic, therefore, cannot be adequately covered in a single review. The objective of this review is to discuss strategies in current use to prevent breast cancer, as well as potential approaches that could be used in the future. This review does not discuss early detection strategies for breast cancer, including breast cancer screening. The breast is the most common site among women worldwide of noncutaneous cancer. Many clinical and genetic factors have been found to increase a woman's risk of developing the disease. Current strategies to decrease a woman's risk of developing breast cancer include primary prevention, such as avoiding tobacco, exogenous hormone use and excess exposure to ionizing radiation, maintaining a normal weight, exercise, breastfeeding, eating a healthy diet and minimizing alcohol intake. Chemoprevention medications are available for those at high risk, though they are underutilized in eligible women. Mastectomy and/or bilateral oophorectomy are reasonable strategies for women who have deleterious mutations in genes that dramatically increase the risk of developing cancer in either breast. There are a variety of strategies in development for the prevention of breast cancer. Personalized approaches to prevent breast cancer that are being developed focus on advances in precision medicine, knowledge of the immune system and the tumor microenvironment and their role in cancer development. Advances in our understanding of how breast cancer develops are allowing investigators to specifically target populations who are most likely to benefit. Additionally, prevention clinical trials are starting to evaluate multi-agent cancer prevention approaches, with the hope of improved efficacy over single agents. Finally, there is a push to increase the use of chemopreventive agents with proven efficacy, such as tamoxifen and raloxifene, in the prevention of breast cancer.

Keywords: Breast cancer, biomarkers, carbohydrates, proteins, DNA, RNA

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Introduction

While breast cancer death rates increased by 0.4% per year in the United States (U.S.) between 1975 and 1989, between 1989 and 2015 they decreased by 39%, averting 322,600 deaths (1). There has not been a similar decrease in breast cancer incidence. The incidence of breast cancer is increasing in the developing world due to increased life expectancy, increased urbanization and the adoption of western lifestyles (2). There is an emerging epidemic of obesity related cancers, including breast cancer, in many parts of the developed and developing world. The incidence of obesity related cancers (other than those of the colon and rectum) increased in the U.S. by 7 percent between 2005 and 2014, while the rates of non-obesity related cancers declined during that time (3). About 631,000 people in the U.S. were diagnosed with a cancer associated with overweight and obesity in 2014 (3).

The prevention of breast cancer depends on targeting factors that increase risk. Many, but not all of these risk factors can be modified. Those that can be modified include diet; exercise; avoidance of certain things such as tobacco, exogenous female hormones, ionizing radiation, and alcohol in excess; pregnancy and nursing. An important question when discussing breast cancer prevention is which individuals to target. In general, greater focus has been placed on strategies to decrease risk among those at the greatest risk of developing breast cancer. For high risk women, two chemoprevention medications have been approved by the U.S. Food and Drug Administration (FDA), and a third recommended by some governing bodies for use. Surgery has also been recommended for certain subsets of women who are genetically at increased breast cancer risk.

Risk factors are inherited, histopathologic or environmental, each of which is important. Strategies to decrease environmental risks generally focus on directly addressing the environmental factor, whereas genetic and histopathologic risks, which cannot so easily be altered directly, are addressed indirectly, such as through altering known drivers to breast cancer, such as estrogen and its receptor through chemoprevention, or by surgical extirpation of the organ(s) at risk. Mammographic breast density (MBD) also influences breast cancer risk. MBD is appears to be influenced by genetics (4), age and body mass index (5).

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There are a variety of risk assessment tools available, some of which require information on breast cancer (*BRCA*) gene mutation status, and others which do not but rather focus on clinical and histopathologic factors which influence risk (6). The Gail breast cancer risk assessment tool (BCRAT) is the tool most commonly used in the U.S. to estimate a woman's risk of developing breast cancer. This tool was used to determine eligibility in two large U.S. breast cancer prevention trials (the first evaluating tamoxifen, the second tamoxifen vs. raloxifene) (7). It incorporates a variety of clinical and histopathologic factors. Two European breast cancer prevention trials (the first evaluating tamoxifen, the second anastrozole) used the Tyrer-Cuzick risk assessment tool, which incorporates genetic and clinical breast cancer risk factors (7).

Scientists have identified some of the genetic mutations which drive the development of breast cancer, but we know relatively little of genetic alterations which work together, or in concert with environmental alterations, to promote breast cancer development. Some of the proven or potential driver genetic alterations, including *BRCA 1* and *2, TP53, PTEN, STK11, CDH1, PALB2, CHECK2, ATM, NBN,* and *NF1* (8), are included in commercially available risk assessment panels. Genetic counseling can be provided to discuss detection of one or more alterations in a driver mutation, as well as the implications of an identified deleterious mutation and a patient's options.

Male breast cancer (MBC) accounts for fewer than 1% of all cancers in men and is less than 1% as common as female breast cancer (9). Due to the relative rarity of MBC, far less is known about what causes the disease, and chemoprevention studies have generally excluded men from enrollment. Nonetheless, limited studies have provided evidence for the causes of MBC. A report which pooled data from 11 case-control and 10 cohort studies, including 2,405 men with and 52,013 men without breast cancer, demonstrated that risk factors for MBC include obesity (odds ratio-OR=1.3), diabetes (OR=1.19), Klinefelter syndrome (OR=24.7), and gynecomastia (OR=9.78) (10). Many of these factors lead to elevated levels of circulating estrogen. Family history is also an important risk factor for MBC. Deleterious mutations in *BRCA1* and *2* are known to significantly increase the risk of MBC. Lifetime risk of developing MBC is 1–5 % for *BRCA1* and 5–10 % for *BRCA2* mutation carriers, compared with a risk of 0.1% in the general male population (9).

Currently Accepted Targets for Breast Cancer Prevention

1. Primary prevention

A. Dietary modification

Obesity is a common cause of many cancers, including those of the breast, endometrium, ovary, prostate, liver, gallbladder, kidney and colon (11). How specific foods influence breast cancer risk, independent of weight gain or loss, is less certain (12). Obesity is associated with a higher risk of premenopausal estrogen receptor negative breast cancer and triple negative breast cancer (TNBC), with two meta-analyses of women with TNBC demonstrating an 80% and 43% higher risk of developing TNBC, respectively, in obese than in non-obese premenopausal women (13). Between 2011-2014 over one third (36.5%) of U.S. adults were reported to be obese (BMI≥30) (14), with rates higher among women than men. The prevalence of obesity was lowest among Asian (11.7%) and highest among black (48.1%) adults (14). The prevalence of obesity among children aged 2-10 years was 17% (14). The prevalence of obesity continues to increase among adults (from 30.5% in 1999 to 37.7% in 2014), though youth obesity may be leveling off (14).

Many U.S. adults who are not obese are overweight (BMI 25-29.9). Estimates in 2015 suggested that 40% of men (36.3 million) and 29.7% of women (almost 28.9 million) were overweight. Combined with the percent of obese individuals, in 2015 more than two thirds of U.S. adults were overweight or obese (15). These trends are also seen in other parts of the world, and worldwide obesity has nearly tripled since 1975 (11). In 2016, the World Health Organization reported that 1.9 billion adults and 381 million children aged 2-19 years were overweight or obese (11).

B. Exercise

Exercise appears to be safe for most breast cancer patients, and improves their physiological and psychological well-being (16). Assessment of the benefits of exercise in the prevention of breast cancer are often confounded by the effects of concomitant weight loss or gain. A meta-analysis of prospective studies which evaluated the association between physical activity and breast cancer risk involving 63,786 individuals demonstrated a 12% reduction in risk among those who were physically active vs. those who were not (17). Stronger associations with physical activity and breast cancer risk were found for subjects with a BMI <25 (hazard ratio: HR=0.72), premenopausal women (HR=0.77), and estrogen and progesterone receptor-negative breast cancer (HR=0.80).

C. Tobacco and alcohol

Tobacco use is a leading cause of cancer incidence and death from cancer (18). Tobacco use causes cancer of the lung, larynx, mouth, esophagus, throat, bladder, kidney, liver, stomach, pancreas, colon and rectum, and cervix, as well as acute myeloid leukemia. Studies evaluating a possible association of tobacco use with breast cancer have demonstrated mixed results. This may be due to the confounding of alcohol use. Most reports indicate that alcohol use increases breast cancer risk (19). A longitudinal study was conducted by the American Cancer Society involving over 70,000 women with a median follow-up of 13.8 years in which concomitant alcohol use was considered. The analysis demonstrated that breast cancer incidence was 24% higher among smokers than non-smokers and 13% higher in former smokers than non-smokers (20), with a stronger association between smoking and breast cancer risk among women who started smoking before the birth of their first child. The positive association between smoking and breast cancer risk was seen in current or former alcohol drinkers, but not in those who never drank.

D. Exogenous use of estrogens and progestins

The role of exogenous female hormones in the development of breast cancer remains uncertain, though most reports of the use of combined estrogen and progesterone formulations after menopause report an increased risk of breast cancer. The use of estrogen alone after menopause, which is only safe among women who have undergone hysterectomy (for estrogen alone use increases the risk of endometrial cancer), does not appear to increase a woman's risk of developing breast cancer (21).

Findings regarding birth control pill (BCP) use and breast cancer risk are mixed, but the bulk of evidence suggests that BCPs increase risk during active use, which decreases over time once BCP use is stopped (22). Many have believed that the mixed findings regarding BCPs and breast cancer risk are related to the BCP dose, suggesting that higher doses of estrogens and progestins are more likely to increase breast cancer risk. Higher doses of female hormones were more commonly present in BCPs that were prescribed in the past than in BCPs in current use. However, a recent study which followed 1.8 million women in Denmark who

used contemporary hormonal contraceptives demonstrated that BCPs and IUDs which release progestins increased a woman's risk of breast cancer on average by 20%. Different hormonal formulations did not appear to significantly alter the increase in risk (23).

E. Ionizing radiation

Most cancers can be induced by ionizing radiation, with a linear dose-response noted for most solid cancers (24). As there is generally a time lag of five or more years between exposure and the development of radiation induced cancer, many of the most revealing studies have been performed in children and young adults who received radiation for the diagnosis and treatment of cancer. The most radiosensitive organ sites in children, in order of sensitivity, are the thyroid gland, breasts, bone marrow, brain and skin (25). At one time, infants received radiation to treat certain benign lesions (hemangioma and an enlarged thymus). Infants who received on average 30 cGy to treat an hemangioma had a 40% increased risk of breast cancer while those who received 70 cGy to treat an enlarged thymus had a 250% excess risk of developing breast cancer (25). The excess risk persisted for up to 50 years after the radiation exposure.

Studies of radiation exposure from multiple chest X-rays used to monitor treatment for tuberculosis (TB) in adolescent girls and young women and a study of multiple X-ray examinations to monitor curvature of the spine in girls with scoliosis have reported increased mortality from breast cancer with increasing radiation dose, with the increased breast cancer risk appearing 15 years after radiation exposure and the risk remaining elevated up to 50 years later (24).

Young women who receive computerized tomography (CT) scans of the chest or heart may also be at increased breast cancer risk. The records of almost a quarter of a million women, who underwent imaging between 2000 and 2010, were reviewed and breast cancer risk determined. Those who underwent CT or nuclear medicine scans which exposed breast tissue to radiation were compared to National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) breast cancer risk data (control). The authors concluded that a child or young adult under the age of 23 who received two or more chest or cardiac CTs had more than double the normal 10 year risk of developing breast cancer (26).

Therapeutic radiation to treat a childhood cancer is also associated with increased breast cancer risk. An assessment of 1,230 female childhood cancer survivors treated with chest irradiation demonstrated that by age 50 years the incidence of breast cancer was 30% overall, and 35% among those receiving radiation to treat Hodgkin's lymphoma (27). This is compared to a lifetime breast cancer risk of 12.4% in otherwise healthy women (28).

F. Pregnancy and nursing

Immediately following childbirth there is an increased risk of breast cancer observed for women of all age groups. Over the long term, parity is protective for women whose first full term pregnancy (FFTP) was completed at a young age (<26), and increased in parous women whose FFTP occurred after 35 years of age (29). Breast cancer diagnosed shortly after childbirth tends to be aggressive. It is more likely to be hormone-insensitive, higher grade, with a higher proliferative rate (30) and a higher likelihood of bone marrow metastases (31).

Observational studies have demonstrated inconsistent findings regarding nursing, length of nursing and risk of premenopausal breast cancer. A prospective cohort study, part of the Nurses' Health Study II, involving 60,075 women demonstrated an inverse association (HR=0.75) between having ever breastfed and risk of premenopausal breast cancer (32). There was no association between length of lactation and risk. Subset analysis demonstrated that the influence of lactation on premenopausal breast cancer risk was limited to women at increased breast cancer risk because of a first degree relative who had developed breast cancer (HR=0.41). There was no association between lactation and breast cancer risk among women of normal risk.

2. Chemoprevention

A. Overview

Two selective estrogen receptor modular (SERM) medications, tamoxifen and raloxifene, are approved by the FDA to prevent breast cancer in high risk women. In the studies which helped support FDA approval, high risk was defined as women 60 years or older, 5-year risk of invasive breast cancer ≥1.67% or lifetime breast cancer risk of at least 20% of developing invasive breast cancer based on the BCRAT (7). SERMs act as an anti-estrogen in some organ systems, and in a pro-estrogenic fashion in others. Tamoxifen was the first agent to be approved, and the only one approved for use in both pre- and post-menopausal women. The Breast Cancer Prevention Trial, started in 1992 and funded by the U.S. National Cancer Institute, enrolled 13,388 pre- and post-menopausal women deemed to be at increased breast cancer risk. Approximately equal numbers of women received tamoxifen or placebo. Tamoxifen reduced the risk of invasive breast cancer by 49% overall and in all age subgroups by over 40% (33). It also reduced the incidence of ductal carcinoma *in situ* (DCIS) by 50%, lobular carcinoma in situ (LCIS) by 56% and atypical hyperplasia by 86%. Tamoxifen also reduced the number of hip, radius and spine fractures. On the other hand, there was an increased risk of developing endometrial cancer, stroke, pulmonary embolism, and deep vein thrombosis. The risk of developing one or more of these side effects was higher in women over age 50. The International Breast Cancer Intervention Study (IBIS)-I clinical trial based in Europe, used the Tyrer-Cuzick risk assessment tool and required that women have a 10 year risk of developing breast cancer of at least 5% (7). The study enrolled 7.154 pre- and post-menopausal women deemed to be at increased risk of developing breast cancer. They were randomized to tamoxifen or placebo. Long term follow-up (median 16 years) demonstrated that tamoxifen decreased the risk of breast cancer (HR=0.71) overall, estrogen receptor (ER) positive invasive breast cancer (HR=0.66) and DCIS (HR=0.65), but not invasive ER negative breast cancer (34).

Raloxifene was approved based in part on findings from a prospective, randomized trial that by compared the agent to tamoxifen. At the time the trial started, raloxifene was already FDA approved to treat osteoporosis in postmenopausal women. Therefore, the trial comparing raloxifene to tamoxifen enrolled only postmenopausal women. Among the 19,747 women enrolled, median age was 58.5 years. The risk of developing invasive breast cancer was similar between the two agents, though there were 40% fewer cases of DCIS in the tamoxifen group (35). There was a 38% lower incidence of uterine cancers (HR=0.62), thromboembolic events (HR=0.70) and cataracts (HR=0.79) in the raloxifene group.

In 2013 the American Society of Clinical Oncology issued and updated guideline on interventions to reduce the risk of breast cancer in women at increased risk for the disease. The guideline was the third addressing the use of chemopreventive medications in women at increased breast cancer risk, and the first to recommend discussing

the option of exemestane, an aromatase inhibitor, as an alternate to tamoxifen or raloxifene in postmenopausal high risk women (36). In the MAP.3 trial, exemestane was compared with placebo or celecoxib plus exemestane in 4.560 postmenopausal women deemed to be at increased breast cancer risk (37). Exemestane (plus or minus celecoxib) decreased the risk of ER positive (HR=0.27) but not ER negative (HR=0.80, but p>0.05) invasive breast cancer. DCIS incidence was lower with exemestane (HR=0.65), but the difference did not reach statistical significance. The IBIS II trial recruited postmenopausal women from 18 countries in a prospective randomized study comparing another aromatase inhibitor, anastrozole, vs. placebo. After a median follow-up of 5 years, anastrozole decreased the risk of developing breast cancer (HR=0.47) (38).

B. Specific subgroups: histopathologic alterations and breast density findings which increase risk

There are many benign breast disease alterations identified on needle or excisional breast biopsy which have been associated with increased breast cancer risk. In general, these alterations can be separated into hyperplasia (usual or atypical) and LCIS. The risk of developing breast cancer in women with usual hyperplasia is increased 50-100%, whereas atypical hyperplasia of the breast increases risk 4-5 fold (39), or 1.5-2% per year (40). The risk of breast cancer development in patients with LCIS is 2% per year, compared to the risk in otherwise healthy women of < 0.4% per year (41). Women with atypical hyperplasia or LCIS have a greater than 30% lifetime risk of developing breast cancer (42). There are few indicators in these high-risk women which assist the treating healthcare provider in determining if the patient will develop invasive breast cancer, with the possible exception of the extent of disease. Greater disease extent increases risk both for women diagnosed with atypical hyperplasia (43) and LCIS (41). The lack of clarity regarding which individuals with atypical hyperplasia and LCIS will go on to develop breast cancer is a problem when counseling women regarding risk reduction, since chemoprevention and surgical strategies have the potential for side effects. Moreover, while bilateral mastectomy is an option for those with LCIS, it is not generally recommended when one is diagnosed with atypical hyperplasia.

Women with dense breasts on mammogram have an increased risk of developing breast cancer, and increased density makes breast cancer detection when reading two dimensional mammograms more difficult (44). However, it is not clear if reducing MBD reduces risk. The chemopreventive agent tamoxifen was evaluated for its potential ability to reduce MBD in women at increased breast cancer risk. MBD measurements were obtained before starting tamoxifen or placebo and on treatment at 12- to 18-month intervals. A reduction in MBD was noted within 18 months of tamoxifen treatment, which lasted for at least 54 months. After 54 months on tamoxifen, MBD decreased on average 13.4% in women 45 years or younger at entry vs. 1.1% in women over 55 years at entry (45). it is not clear that this risk reduction is due to tamoxifen's effect on MBD, on other breast cancer risk factors, or both (44). It appears that the influence of MBD on breast cancer risk is primarily in women with non-proliferative breast disease, with little influence on future risk among women with atypical hyperplasia (46).

3. Surgical approaches to breast cancer prevention: mastectomy and/or oophorectomy

Among the breast cancer driver genetic mutations that have been identified, including *BRCA 1* and *2, TP53, PTEN, STK11, CDH1, PALB2, CHECK2, ATM, NBN,* and *NF1* (8), each alteration imparts its own unique implications regarding future breast cancer risk. Guidelines as to which therapies are reasonable are based on known risk implications. Guidelines are updated from time to time based on the latest available information. Current recommendations from the American Society of Breast Surgeons is that risk reducing bilateral mastectomy is a reasonable approach for women without breast cancer who have a known deleterious mutation in *BRCA 1, BRCA2, TP53, PALB2, CDH1,* or *PTEN*. Risk-reducing mastectomy is recommended for consideration for patients with deleterious mutations in *CHEK2* or *ATM* if the patient has a family member with breast cancer (8). Increased surveillance with breast MRI and mammogram, but not bilateral risk-reducing mastectomy, is recommended for patients with mutations in *STK11, NF1,* and *NBN*. Screening is recommended to start at age 30 for *STK11* and *NF1*, and at age 40 for *NBN* (8).

Bilateral risk-reducing mastectomy is also recommended for consideration in women with a history of prior therapeutic mantle radiation (47) and with a diagnosis of LCIS. An additional option for risk reduction in those diagnosed with LCIS is chemoprevention, as tamoxifen was shown to decrease the risk developing breast cancer in this population of women (33). Mastectomy is not recommended as a routine procedure for risk reduction in the contralateral breast of women diagnosed with cancer in the ipsilateral breast, but may be discussed with the patient based on individual risks and benefits, such as a strong family history and a known deleterious genetic mutation which increases breast cancer risk (48). Alternatives include chemoprevention, which reduces the risk of contralateral breast cancer in women diagnosed with cancer in the ipsilateral breast, including women demonstrated to carry a deleterious *BRCA1* or *BRCA2* mutation (49).

Bilateral salpingo-oophorectomy (BSO) can be considered for risk reduction in genetically high-risk women. BSO reduces breast cancer risk in premenopausal *BRCA 1* and *2* mutation carriers by approximately 50%, similar to tamoxifen, compared to a 90% reduction in similar women who undergo bilateral mastectomy (50). BSO also reduces the risk of ovarian cancer in these women by 90% (51).

The Future of Breast Cancer Prevention

Innovations have greatly advanced our understanding of breast cancer. These innovations have driven a precision based, patient focused approach to the treatment of breast cancer. These same and similar innovations are driving the future of breast cancer prevention.

1. Precision medicine

The ability to sequence a patient's entire genome from a blood or tissue sample has dramatically improved in recent years. Multiple companies and cancer centers now offer whole genome sequencing of a patient's tumor to identify targetable mutations for treatment, and increasingly treatment trials are being designed based on a given genetic alteration rather than on the site of tumor origin. The NCI has launched a clinical trial called NCI-Match, in which patients are assigned treatment based on the genetic changes found in their tumors rather than on disease site (52). The origin of cancer can be from a variety of tumor sites, including the breast. Gene sequencing laboratories that are participating in the study including Foundation Medicine, Caris Life Sciences, MD Anderson Cancer Center, and Memorial Sloan-Kettering Cancer Center.

Studies have been reported in a variety of cancers addressing how gene alterations may guide chemopreventive strategies. For example, EGFR mutations have been identified in the histologically normal epithelium of patients with lung cancer, and PI3K/AKT activation has been identi-

fied in the airways of smokers with precancerous lesions (53). A cancer prevention trial using myo-inositol in patients with bronchial dysplasia demonstrated significant reductions in the inflammatory cytokine IL-6, though other cancer-associated biomarkers did not significantly change with treatment. Among participants with a complete response in the myo-inositol arm, there was a significant decrease in a gene expression signature reflective of PI3K activation (p=0.002) (54). Investigators of the study suggest that a more detailed assessment of molecular alterations in the bronchial tissue may identify additional alterations which could be targeted and hopefully increase the efficacy of myo-inositol as a chemopreventive agent. Future studies which emphasize molecular approaches to breast cancer chemoprevention are likely.

The NCI has issued a request for applications (RFA) for Pre-Cancer Atlas Research Centers (RFA –CA-17-035) (55). This call is a companion to CA-17-034, Human Tumor Atlas Research Centers. In the pre-cancer atlas RFA, the NCI is looking for proposals that focus on a multidimensional cellular, morphological and molecular mapping of human pre-malignant tumors, complemented with critical spatial information (at the cellular and/or molecular level) that facilitates visualization of the structure, composition, and multiscale interactions within the tumor ecosystem over time resulting in tumor progression or regression. The RFA posits that a deeper understanding of the transition from the pre-malignant to the malignant state as a function of time will allow the development of more precise risk stratification methods and effective early intervention strategies.

2. Immunoprevention

The immunoprevention of cancer has been in place for some time with the use of cancer vaccines. A vaccine to the hepatitis B virus produced an 80% reduction in the development of hepatocellular cancer in Taiwan (56). A three-dose prophylactic vaccine to human papilloma virus (HPV) is 90-100% effective in preventing HPV infection and associated anogenital malignancies (53). Fewer doses may be as effective as the three-dose regimen.

Vaccines to prevent non-viral induced cancers is an attractive approach to cancer prevention. A validation study is underway targeting MUC1 for the primary prevention of colon cancer based on initially promising results (57). Preliminary results evaluating a HER2 vaccine for the prevention of recurrence in women with a history of HER2 positive breast cancer were also encouraging (58). Vaccines which induce immunity to multiple antigens are in development as well, and may be more effective than single agent vaccines in activating the immune system to target premalignant lesions of the breast (59).

3. Tumor microenvironment (TME)

The TME appears to be altered early on in the development of cancer (53). The microenvironment becomes immunosuppressive such that immunoprevention strategies are less effective. Checkpoint inhibitors (targeting CTLA-4, PD-1, PD-L1 and PD-L2), have been effective in decrease the immunosuppressive TME when cancer is present. These agents are rather toxic, however, and therefore other strategies, such as depleting suppressive T cells (Tregs), may be better (53) for enhancing vaccine and other immunoprevention strategies.

4. Targeting specific populations

Cancer prevention currently targets high risk individuals, based on known risk factors such as evidence of a deleterious mutation in a breast cancer oncogene (e.g. *BRCA1* and *2*), family history, and breast biopsy premalignant changes. A high-risk population that has been targeted to a lesser degree are individuals who are obese. This is starting to change. The NCI is funding a study to determine if metformin, an FDA approved medication for the treatment of diabetes which has shown preliminary promise as a cancer preventive agent, will decrease the risk of obesity related postmenopausal breast cancer (NIH grant no. R01CA172444-05).

5. Single vs. multiple agents

Demonstration and validation of the safety and efficacy of a single agent, or at least preclinical evidence for synergy among two or more agents with evidence of clinical safety, is generally a pre-requisite to the initiation of a multiple agent clinical study. It is therefore perhaps not surprising that the vast majority of chemoprevention clinical trials conducted thus far have evaluated single agents. Cancer treatment is generally more effective when targeting multiple driver pathways with multiple agents, as opposed to only one. It is likely that this is also true for precancers. Findings from a lung cancer prevention trial involving the administration of myo-inositol vs. placebo in smokers with bronchial dysplasia demonstrated an effect on the targeted PI3K/Akt pathway, but limited to no effect on other affected pathways, leading to no overall improvement in response with active agent vs. placebo (54). A recent randomized clinical trial showed increased efficacy of combination chemoprevention in patients with familial adenomatous polyposis which targeted two pathways, Wnt/EGFR and COX, using sulindac and erlotinib vs. either agent alone (60).

6. Increasing the use of agents proven effective in preventing breast cancer

As previously mentioned, there are two agents (tamoxifen and raloxifene) currently approved for the prevention of breast cancer in postmenopausal high-risk women. Two aromatase inhibitors, exemestane and anastrozole, also demonstrate promise in preventing breast cancer in this population. Tamoxifen is also FDA approved for the prevention of breast cancer in premenopausal high-risk women. The percentage of eligible women taking a chemoprevention medication to decrease their risk of breast cancer is less than 10% (61). There are a variety of reasons for this. For many women, consideration of chemoprevention is not discussed with them by a healthcare provider (62). Moreover, many are concerned about the potential side effects such as endometrial cancer and blood clots with tamoxifen, others stop the medication because they have experienced a side effect, most commonly hot flashes. Indeed, for individuals who initiate a medication, the most common reason to stop is due to side effects (63). Women less likely to take chemoprevention are older, smokers and those with depression (62).

How to overcome this? There are newer SERMs (arzoxifene, bazedoxifene and lasofoxifene) with evidence of efficacy with a lower risk of side effects than tamoxifen (64). Lowering the dose or intermittent dosing of tamoxifen appears to decrease side effects while maintaining biologic efficacy (7). In a short term pre-surgical window trial, transdermal 4-hydroxytamoxifen applied directly to the breast skin showed promising preliminary evidence of efficacy comparable to oral tamoxifen (65). Transdermal delivery appeared to reduce the systemic effects on endocrine and coagulation parameters, though the incidence of hot flashes was similar in both groups.

Summary

We are already aware of important risk factors that lead to cancer (smoking, obesity, lack of exercise, high alcohol intake) which are being addressed, with some success. To increase our impact on cancers that are caused by these behaviors, we need to overcome the inertia at

a personal and social level with regard to adopting healthy behaviors. Equally important, we need to encourage activities such as breastfeeding that are associated with lower risk of breast cancer, at least among women with a family history of the disease. We need to continue to educate clinicians on the hazards of ionizing radiation, and the adoption of imaging approaches which mitigate this.

Vaccines which prevent cancer must continue to be promoted, and new preventive vaccines developed. We should encourage more women with pathologically precancerous lesions and who are genetically at high risk to consider cancer prevention strategies. This requires that we educate their healthcare providers. It also requires that our interventions be safe, easy to use and with limited side effects.

We need to develop new technologies to better identify women at the greatest risk of developing breast cancer. Atypical hyperplasia places women at significantly increased risk, but we lack clear evidence of which women with this diagnosis will have their disease progress to invasive breast cancer. Surgical risk reduction is currently not recommended for most women who are at increased risk and chemoprevention uptake is not used by most women due to the risk of side effects. We need to develop tools that can better predict which women are at the greatest risk of developing breast cancer so that healthcare providers can better counsel them, and that women can better weigh the risks and benefits of active intervention, such as chemoprevention, vs. observation.

Risk assessment needs to be personalized. There have been many paradigm-changing advances in cancer prevention, and many more to come. Developing safe and effective agents, personalizing preventive therapy, and harnessing technology will be increasingly important in getting public buy-in and achieving greater participation in cancer prevention trials.

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Review

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Echoes from the 40th Annual San Antonio Breast Cancer Symposium, 2017

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ABSTRACT

The Annual San Antonio Symposium was held on 5-9, December, 2017 in San Antonio, Texas, USA (1). As expected, many new studies were presented for the first time at the sessions. The unofficial opening lecture in my point of view was given on locoregional recurrence by Monica Morrow from MSKCC, New York. As always, Morrow's lecture on "Challenges in the surgical management of locoregional recurrence" attracted great interest. The other prominent conferences were given on "Individualizing Management of the Axillary Nodes" by Tari A. King from Dana-Farber Cancer Institute and on "Appropriate margins for breast conserving surgery in patients with early stage breast cancer: A meta-analysis" by Shah C from Cleveland Clinic.

Keywords: Breast cancer, Breast Cancer Symposium, San Antonio

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Morrow reported that changing treatment landscape had raised new questions on axillary management, on initial sentinel lymph node (SN) biopsy and repeat lumpectomy. The important remarks that I selected from her lecture are as follows: Metastatic work up is essential prior to any local therapy for locoregional recurrence (LRR); because, historically ~50% of LRR was accompanied by distant metastases. Axillary dissection is an appropriate approach for axillary recurrence after SN biopsy. Reoperative SN biopsy after local recurrence is feasible, accurate and provides useful information. A SN can be identified in the majority of the patients who had initial SN biopsy (81%), and in about 50% of those with axillary dissection. Aberrant drainage is common after SN or axillary dissection and has implications for mapping. Extra-axillary or aberrant lymphatic drainage is uncommon in untreated axilla. However, in patients with ipsilateral breast recurrence (IBTR) after a breast conserving surgery (BCS) and SN biopsy or axillary dissection, aberrant drainage is likely in one third of patients. Because prior axillary surgery increases drainage to contralateral axilla, this is not necessarily a metastatic disease. In patients who had contralateral axillary metastases identified with ipsilateral local recurrence, Morrow suggested to do metastatic work-up and to exclude contralateral breast primarily with mammography and magnetic resonance imaging, and if local recurrence was operable and non-locally advanced, to perform axillary dissection. Combined radioactive colloid and blue dye is recommended for reoperative SN biopsy, because identification of extra-axillary SN is uncommon with intradermal or subareolar injection. She suggests peritumoral injection is optimal in reoperative setting. Under the heading of 'Management of IBTR after BCS: Is lumpectomy alone appropriate?', the indications for repeat lumpectomy alone were suggested as follows: disease meeting criteria for no radiotherapy after primary surgery (that is, low risk group); age >70 years, T1N0 ER+ Her2-, Grade 1, 2 DCIS ≤1.5 cm, disease suggestive of second primary tumor with long disease-free interval, in separate quadrant, and patients with severe morbidity. Morrow concluded that better data were needed to define optimal management of LRR.

Tari King reported that the quest for optimal regional treatment is continuing, and the goal of balancing the risks and benefits of treatment options is to minimize morbidity of local regional treatment without compromising the outcome. Here are the remarks from her lecture: SN after neoadjuvant chemotherapy (NAK) in T1, 2, cN0-cN1 patients decreases axillary dissection significantly due to the decrease in % of node positive axilla. Benefits of avoiding axillary dissection were manifested with lower rates of lymphedema (11-14% for axillary dissection vs. 3-8% with SN). Rationale for NAK in cN+ patients was that nodal pCR rates were 38-49%. Nodal pCR rates were 21% for ER+/Her2-, 47% for ER-/Her2-, 70% for ER+/Her2+, and 97% for ER-/Her2-, respectively. There is no role for nomograms to predict the likelihood of additional axillary metastases or PET scans to look for additional metastases. In response to "When can nodal staging be omitted?", from 'CALGB randomized trial of the omission of radiotherapy', patients with age ≥70 years, T1N0, ER+, patients who had BCS and tamoxifen treatment were suggested as candidates for omission of axillary staging. Ten-year rate of axillary failure for these patients (no: 392) was 1.5%. Tari King concluded under the title of "Where will we go from here" that "there was no improvement on survival with axillary dissection", "Increasing role of biology vs. anatomy in decision making for systemic therapy", and "Growing interest to omit axillary staging".

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Shah reported the results of the new meta-analysis on surgical margin after BCS. He explained the new methods used in the new analysis and compared the findings with the previous meta-analysis by Houssami et al. who concluded that wider than negative margins were unlikely to have substantial local control benefit. Current SS-ASTRO Guidelines for invasive breast cancers with lumpectomy recommends no tumor on ink as the appropriate margin as suggested by the previous meta-analysis of Houssami et al. Shah et al. query for this recommendation and ask the question: "Is this correct?" Instead of two methods used in the previous meta-analysis, they used three methods for margin evaluation. In the third method, i.e., the new one, the margin ranges which were 'no tumor on ink' (indicated as negative margin, 0-2 mm, 2-5 mm, and >5 mm) were used for the analysis. In the new meta-analysis, there were 55.302 patients from 38 studies and >20.00 additional patients with BCS. In multivariate analysis, the margin width was significantly associated with decreased local recurrence when using margin ranges. Data suggests that having a margin width beyond 'no tumor on ink' may further reduce rate of local recurrence. Shah et al. concluded that the new questions were as follows: "Should we achieve a 1-2 mm margin as compared with no tumor on ink?", "What is the local control benefit vs. morbidity, time, cost?", and "Which patients with 'no tumor on ink' need more surgery?"

Among more than 1400 poster presentations, there were three poster presentations from Turkey. Two of the posters were presented by Guldeniz Karadeniz Çakmak from Bülent Ecevit University, School of Medicine, Zonguldak and the third was presented by Bekir Kuru from Ondokuz Mayıs University, School of Medicine, Samsun.

Karadeniz Çakmak et al. (2) reported on the first poster that in 194 patients treated with breast conserving surgery after neoadjuvant chemotherapy, continuous intraoperative ultrasound with specimen sonography was an invaluable and effective modality to achieve negative surgical margins. Karadeniz Çakmak et al. (3) concluded on the second poster that a study performed on 69 patients showed that surgeon performed axillary ultrasound was a beneficial tool with the potential of accurate prediction of axillary disease in up to 78% of patients after neoadjuvant chemotherapy.

Kuru et al. (4) studied 440 patients with ductal carcinoma in situ (DCIS) associated with invasive breast carcinoma (IBC) among 628 T1-2 IBC patients and concluded that 'no ink on tumour' was an adequate margin for DCIS associated with IBC in patients who underwent breast conserving therapy and was not associated with increased ipsilateral breast cancer recurrence.

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Review

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Surgical Highlights from the 40th San Antonio Breast Cancer Symposium: 5-9 December 2017, San Antonio, Texas

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ABSTRACT

This year San Antonio Breast Cancer Symposium (SABCS) celebrated its 40th anniversary. As in the past years, this year's conference was held in Henry B. Gonzalez Convention Centre, San Antonio, Texas, on 5-9 December 2017. The conference highlighted many different topic on breast cancer including basic science, translational research, local therapies, systemic therapies, survivorship, early clinical trials, and surgical topics. Even though SABCS evolved towards basic science and systemic therapy based manner in recent years, there were some important topics about local therapies and surgical approach. In this conference report, presentations and keynote talks about surgical field and local therapies will be summarised.

Keywords: Axilla, breast neoplasm, San Antonio, sentinel lymph nodes, survival

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Introduction

San Antonio Breast Cancer Symposium (SABCS), which is the largest breast cancer meeting in the world, was held in Henry B. Gonzalez Convention Center, San Antonio, Texas, on 5-9 December 2017. This was the 40th anniversary of SABCS. More than 7000 clinicians and scientists from over 90 different countries attended the symposium. The symposium topics ranges from genetic and immunologic studies to surgical fields. As we consider most of the recent ongoing studies about breast cancer are oncological and immunological studies, majority of the presentations and keynote talks were highlighted these topics. Besides important sessions and keynote talks, there were many crucial posters presented in the poster sessions. In this conference report, we want to highlight surgical issues and the presentations that are related directly with surgical practice change. To ensure the integrity and clarity, instead of highlighting day by day, this conference report will be presented under the main subheadings as High-Risk Lesions, Genetics, Breast and Axilla, Screening and Diagnosis, and Other.

High-Risk Lesions

In the first day of the congress, Amy Degnim (Professor of Surgery, Mayo Clinic, United States) placed the focus on clinical management of women with increased breast cancer risk based on histologic lesions. High-risk breast lesions were defined as atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), atypical lobular hyperplasia (ALH), and lobular carcinoma in-situ (LCIS).

There are 2 main questions to be answered in the management of high-risk breast lesions:

1) Should we excise the lesion after core biopsy?

2) How high is long-term breast cancer risk?

According to American College of Radiology guideline, concordance between radiology and pathology needs to be assessed when high-risk lesions were detected. American Society of Breast Surgeons recommendations for excision are if there is a concern that target lesion was missed, if histology demonstrates atypia in presence of a palpable or imaging mass lesion, and if there is a discordant finding. Dr. Degnim summarized the management of high-risk lesions as below:

ADH: Published data shows 13-31% upgrade rates to cancer with an average rate of 15-25%. The **National Comprehensive Cancer Network** (NCCN) guideline recommends excision of ADH. Only a small group of patients with low risk (no concordant mass, small

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lesion size, complete or near complete removal with biopsy) may not require further excision.

FEA: It is usually associated with calcification (>90%) and ADH (27-53%) (1). Published data shows 0-17% upgrade rates to cancer, average of 7%. Most recent studies show lower upgrade rates with an average of 5%. Two-thirds of the lesions upgrade to ductal carcinoma in-situ (DCIS). Besides, FEA can upgrade to another high-risk lesion (ALH or LCIS) by 36%. Excision depends on clinical context. Patients with low risk criteria including having a small lesion (<1cm) and/or without accompanying mass, and if over 90% of the lesion is removed by core biopsy, may be considered for observation.

ALH/LCIS: Recent studies show <10% upgrade rates. Upgrade rates for lobular neoplasia is 3-4%, pure ALH is 0-19% and 7-28% for LCIS. Dr. Degnim briefly stated that these lesions should be excised in the presence of an accompanying mass or radiological-pathological-clinical discordance with high-risk lesion.

The second part of her presentation was about how to predict who is at high risk. There are four categories of lifetime breast cancer risk: Average (≤15%), moderate (16-25%), high (25-50%), and very high (>50%). Lifetime risk is highly dependent on patient age and life expectancy. Long-term absolute invasive cancer risk per year for FEA is 0.5%, ADH and ALH is 1-2%, and LCIS is 2%. Management and follow-up should be individualized depending on annual absolute breast cancer risk, volume of the disease, life expectancy, and competing morbidities. Taking side effects into account prevention therapy (tamoxifen, raloxifene, anastrozole, exemestane) is advised if the patient has >1% per year breast cancer risk or has ADH or LCIS. Risk reduction mastectomy can achieve 90-95% risk reduction and should be considered if other high-risk factors exists (genetics, very high-risk family history, etc.).

Genetics

Dr. Garber highlighted factors for reconsideration of genetics evaluation and testing in her oral presentation on management of increased breast cancer risk based on high and moderate penetrance gene. She discussed the recent update by Kuchenbaecker KB et al. (2) about cumulative risk of breast cancer and ovarian cancer among patients with *BRCA1* and *BRCA2* mutation carriers. The cumulative risk of breast cancer by age 80 years was 72% (95% CI, 65%-79%) for *BRCA1* carriers and 69% (95% CI, 61%-77%) for *BRCA2* carriers. While the cumulative risks for *BRCA1* and *BRCA2* carriers to age 80 years were similar, the cumulative risks to age 50 years were higher for *BRCA1* carriers (p=0.03). The cumulative risk of contralateral breast cancer for *BRCA1* carries 20 years after the first breast cancer diagnosis was 40% (95% CI, 35%-45%). For *BRCA2* carriers, the cumulative risk of contralateral breast cancer at 20 years after the first breast cancer diagnosis was 26% (95%CI, 20%-33%). The ovarian cancer cumulative risk to age 80 years was 44% (95%CI, 36%-53%) for *BRCA1* carriers and 17% (95% CI, 11%-25%) for *BRCA2* carriers. Modified NCCN management guidelines for *BRCA1/2* mutation carriers recommends annual (biannual depending on patient) screening starting at the age of 25.

As multigene tests are becoming more popular, Dr. Garber outlined elevated breast cancer risk for women with moderate penetrance mutations in selected genes such as PALP2, CHECK2, and TAM/NBN. PALB2 and TAM/NBN have cumulative lifetime risk of 44% and 30% respectively. Depending on the pathogenic mutation, CHEK2 has a risk of up to 31.8% for breast cancer. Physicians also must be aware of other associated cancers like pancreas cancer, colon cancer, etc. These patients should be started annual examination at age 40 while the age should be 30 for starting screening for patients with PALB2.

Breast and Axilla

Dr. Morrow mainly focused on challenges in the surgical management of locoregional recurrence. Due to the changes in the management of axilla and breast in recent years, Dr. Morrow raised new questions about loco-regional recurrence, how to manage axilla in the setting of axillary dissection was not initially done and secondly whether repeat lumpectomy without radiotherapy (RT) is appropriate.

There are three issues about axilla:

1) Management of nodal recurrence after sentinel node biopsy (SNB).

2) Management of the axilla and nodal re-staging after breast or chest wall recurrence.

3) Significance of contralateral axillary metastases after local recurrence (LR).

First step of managing LR is excluding distant metastasis, as almost 50% of the LR accompanied by distant metastases. Isolated axillary recurrence occurs in <0.6% after negative SNB and 1.1% after positive SNB without axillary lymph node dissection (ALND) with whole breast radiation. Study from the Dutch Cancer Registry about axillary recurrence after negative SNB between 2002 and 2004 showed the median time to recurrence was 30 months (3). Fourteen percent accompanied with distant metastasis. Five-year overall survival (OS) and disease-free survival (DFS) of patients is approximately 60% and 55%, respectively. ALND is suggested for surgical treatment of isolated axillary recurrences, and RT is indicated according to the findings of ALND and initial therapy. When there is an isolated supraclavicular recurrence without distant metastasis, data from Danish Breast Cancer Group Trials suggests that patients who receive both local and systemic therapy has statistically significantly survival improvement (4).

Subsequently, Dr. Morrow addressed two questions on reoperative SNB after LR. Is it feasible and accurate, and does it provide useful information to manage patients? Study from Memorial Sloan-Kettering group about reoperative SNB for patients that initially had breast conserving surgery (BCS) with negative SNB or ALND less than 10 nodes removed showed that sentinel nodes were identified in 55% (n=63) of 117 patients, and 16% (n=10) of them had nodal metastasis (5). Success of reoperative SNB significantly higher if patients initially had SNB rather than ALND and did not have RT. Success of reoperative SNB decreases as the initial number of removed sentinel nodes increases (80% for 0-2 nodes removed, 53% for 6-8 nodes removed). Location of the reoperated sentinel nodes in lymphoscintigraphy presented 70% in ipsilateral axilla only and 30% in non-axillary region (mainly internal mammary node followed by contralateral axilla). Reoperative SNB can be conducted after recurrences of mastectomy patients. Dual tracer application with injection of tracers to upper skin flap can detect sentinel nodes up to 65%. In the systematic review of 692 reoperative SNB patients by Maaskant-Braat A., 301 of them had SNB and 361 had ALND for axilla, and 574 of them had BCS±RT for the breast as the initial surgery (6). The author showed that, identification rates are higher in SNB patients as initial surgery and there is no difference between BCS and mastectomy patients. Aberrant drainage rates for

successfully mapped patients are 26% for prior SNB group and 74% for ALND group. Accuracy and outcomes of reoperative SNB is still scarce due to lack of enough data. Final suggestions about reoperation to axilla is using combined technique with radioactive colloid and blue dye for mapping, and making the injection to peritumoral region.

Identification of nodal metastasis in locally recurrent breast cancer is important because it maintains local control and gives us information about changing RT fields and changing systemic therapy. Contralateral axillary metastasis is defined as stage IV according to American Joint Committee on Cancer classification. Contralateral axillary metastasis constitutes 33% of cases after BCS with ALND. In a systemic review about contralateral lymph node recurrence, >50% of them occurred without ipsilateral breast tumour recurrence (7). Primary treatment was ALND in 71% of patients and almost half of the patients received chemotherapy. Five-year OS is 82.6% and DFS is 65.2% when contralateral axillary recurrence was treated with surgery and systemic therapy.

Dr. Morrow also discussed if lumpectomy alone is appropriate for local recurrence after BCS with RT. She stated that it is not a standard of care and additional local recurrences are high. In her surgical practice, she performs surgery, if patients meet the criteria for no RT after primary surgery (Age>70, cT1N0, ER+HER2- or low-intermediate grade DCIS≤1.5 cm), and if there is a long disease-free interval or tumour occurred to be a second primary.

On the 4th day of the conference, Tari King's speech was probably the most important and controversial recent topic of the breast surgery about individualizing management of the axillary nodes. She started her presentation highlighting to balance the risks and benefits of treatment options between SNB and ALND depending on disease burden, tumour biology, and treatment options like neoadjuvant chemotherapy (NAC). The goal should be minimizing local-regional management without compromising outcomes.

In clinically node positive patients, the choice could be either primary surgery with ALND or NAC followed by SNB for an opportunity to preserve the axilla. In clinically node negative setting, similarly, primary surgery with SNB or SNB after NAC surgical options. According to a meta-analysis, in the setting of clinically node negative patients undergoing NAC, identification rates and false-negative rates are the same for performing the SNB before or after NAC. However, performing the SNB after NAC decreases the needs for ALND (8). In patients with positive axilla after NAC, the standard of care is still performing ALND. In the group of cN0 patients who undergo primary surgery, ALND is still mandatory if the patient has 3 or more involved axillary lymph nodes, whereas patients with 1-2 positive sentinel lymph nodes have the option of axillary observation or axillary RT.

Dr. King then stated important prospective randomized trials about axillary manegament like ACOSOG Z0011, AMAROS, IBCSG 23-01, OTOASOR, and AATRM. In these trials, there is no difference in axillary recurrence rates between ALND and other options (observation or axillary RT). Furthermore, there is no difference in DFS or OS between ALND or observation in Z0011, IBCSG, and AATRM; or between ALND or nodal RT in AMAROS and OTOASAR. The results of POSNAC trial that includes T1-T2 patients with 1-2 sentinel node macrometastasis, who underwent lumpectomy or mastectomy, are awaited. These patients than randomized to systemic therapy alone in one arm and systemic therapy + axillary treatment even with ALND or axillary RT in the second arm. In mastectomy patients, ALND can be avoided if there is a micrometastatic disease and in macrometastatic patients with 1-2 positive lymph nodes with in favor of axillary RT when there is an indication for post-mastectomy RT.

Dr. King than presented Dana-Farber series of mastectomy patients eligible for AMAROS. In this series they looked for predictors of post-mastectomy RT population to spare these patients from routine inrtaoperative assesment of sentinel lymph nodes. They composed a multidiciplinary concensus for mastectomy patients eligible for AMAROS, and suggested not performing intraoperative assesment of sentinel lymph node in patients receiving post-mastectomy RT. Ten-year update results of the Z0011 by Giuliano and colleagues reported again no difference in OS, DFS or loco-regional recurrence between ALND arm and nodal RT group.

In the setting of clinically positive axillary nodes, NAC is a choice for the possiblity of axillary complete response. To evaluate axillary nodes after NAC, at least 3 or more snetinel node sampling with dual tracer is recommended to decrease the false negativitty rates. There are two important ongoing trials about management of the axilla after NAC for patients converted from cN1 to cN0. In the Alliance A11202 trial after NAC, patients with positive SNB were randomized to ALND without axillary RT or no further axillary surgery with axillary RT. In the NRG 9353 trial, patients with negative SNB after NAC were randomized to no regional nodal RT or regional nodal RT. Hormone receptor positive HER2 negative subset is less likely to have positive or high volume nodal disease, and less likely to present pathological complete response so that surgery first is suggested if Z0010 and AMAROS is eligible. For HER2 positive or triple negative group, as they present with reasonable pathologic complete response, principally NAC is considered. In CALGB 9343 trial, patients ≥70 years-old, T1N0, ER+ undergoing BCS followed by tamoxifen treatment, 392 (62%) of these patients had no axillary staging or treatment (9). Ten year axillary failure rate of this subset of group was 1.5% with no differences in OS, DFS or disease specific survival.

Local therapy of limited disease in advanced breast cancer was presented by Dr. Seema Khan from Northwestern University, United States, on educational session about Challenges in Advanced/Metastatic Breast Cancer. She started her talk stating recent clinical data suggest that patients with oligometastasis are potentially curable. So, the question is should we consider surgical resection, RT or other ablative therapies?

Lung metastasis resection series from Institute of Oncology in Milan demonstrated better OS (46% 5-year survival, p<0.0001) and disease-free interval (46.6 months mean DFI) with R0 resection (10). But this was not a pure breast cancer population. Resection for hepatic metastasis from primary breast cancer meta-analysis showed better survival. It also emphasized factors associated with poor survival as disease-free interval less than 4 years, hormone receptor negativity, poor response to chemotherapy, and positive resection margins. There is still no strong data and prospective randomized trials about local therapy for metastatic sites but there is a concensus about those most likely to benefit from ablative therapy. Those are patients with long disease-free interval, metastasis of primary breast cancers, and small number of metastatic lesions (1-3), small sizes of metastasis, and complete ablation of lesions (R0 resection or other means of complete ablation with different interventions like stereotactic body radiotherapy).

Another promising approach for oligometastasis is stereotactic body radiotherapy (SBRT) or hypofractionated image-guided radiotherapy. Milano and colleagues reported a prospective analysis of SBRT for 121 patients with oligometastasis and 39 of them was primarly breast metastasis (11). The most common metastatic sites for breast primary were bone and liver. Overall survival and DFS was better in breast primary group when compared to non-breast group. At a median follow-up of 4.5 years, they achieved 87% local control and 46% 6-years OS.

The approach for primary site of the stage IV breast cancer is also controversial. A meta-analysis that was published in 2012 demonstrated resection of the intact tumor is associated with longer survival but the data of the studies were biased (12). There are two randomised trials in this topic. One is from Turkey and the other one is from India. In the Turkish MF 07-01 trial, unpublished updated data in ASCO 2016 showed significant benefit in 5-year OS and loco-regional progression for local treatment arm (13). In the Indian study, patients were randomized after systemic therapy to loco-regional treatment and no loco-regional treatment (14). They found no survival benefit between two groups but they showed better local control in treated group.

Dr. Galimberti presented ten-year results of the IBCSG 23-01 trial comparing axillary dissection vs. no axillary dissection in patients with cT1-T2cN0M0 breast cancer patients only with micrometastases in the sentinel lymph node. Concordant with the 5-year results, there was no significant difference in DFS, OS, cumulative incidence of breast cancer, and rate of ipsilateral axillary events.

Frank Vicini presented a meta-analysis about appropriate margins for breast conserving surgery in patients with early stage breast cancer. They analysed 38 studies with 55302 patients with a minimum follow-up of 50 months and median of 7.2 years. They utilized 3 different models of analysis. What was different in this study from previous meta-analyses was the second modelling of the analysis. They performed to assess the impact of margin width 'range' rather than a set margin width (≤0mm, 0-2mm, 2-5mm, >5mm). They demonstrated in multivariate analysis that wider margins further reduced local recurrence. In conclusion, Dr. Vicini advocated that data suggest having a margin width beyond 'no tumour on ink' may further reduce rates of local recurrences. He finished his presentation with raising a question as which patient with 'no tumour on ink' need more surgery. At this point a long discussion started because this was an out of guideline suggestion. Dr. Morrow from Memorial Sloan-Kettering criticized about method and possible bias in the meta-analysis. In reply, Dr. Vicini clearly stated that there was no bias in the study, but he finalized his recommendation as wider margins may be necessary for some patients.

Dr. Amit Goyal's keynote talk was about sentinel lymph node mapping. He discussed on three posters about fluorescence techniques, 4 posters about non-operative axillary staging, and 1 poster about intra-operative assessment of sentinel lymph node. He suggested dual agent use as a standard of care for sentinel node mapping with a detection rate of >98% and false negative rate of <10%. However, he also stated that this is practically not so feasible for institutions in non-developed and developing countries. In a systematic review published in 2014, indocyanine green was found better than blue dye and approximately similar with the radioisotope for sentinel node identification (15). A group from Japan and a group from Italy used different real-time methods for sentinel node detection. Japanese group used a medical imaging projection system that is used in liver surgery, and Italian group used laparoscopic camera with a near-infrared filter after injection of indocyanine green. Another new agent for sentinel node detection is 10% fluorescein sodium. It is cheaper than indocyanine green, and does not need expensive devices to track nodes (It only needs goggles with blue light filter). Disadvantage is it has a lower molecular weight than other agents meaning that it can be detected in more sentinel nodes than other agents, leading the surgeon dissect more lymph nodes.

Dr. Goyal started the second part of his talk, which headlined as non-operative axillary staging, by referring the poster of Swedish SCAN-B study. In this study of 3023 patients, they looked for the predictors of axillary nodal metastasis based on gene expression and clinicopathological characteristics. They concluded that clinicopathological factors (age, tumour size, tumour grade, vascular invasion, molecular subtype, etc.) and gene expression, even in combined analysis, are not accurate predictors of nodal metastasis. Another study from Beijing, China retrospectively analysed ultrasonographically node negative women with invasive breast cancer who underwent SNB. Of the 3115 patients, 798 (25.6%) had macrometastasis, and 2317 (74.4%) did not. Even though they found some factors like age and tumour size as significant factors, there was no significance in multivariate analyses. Dr. Goyal concluded his talk stating that two very similar prospective randomized studies are still ongoing about not performing axillary surgery for early stage breast cancer patients in the setting of negative axillary ultrasound. First study is SOUND study, which finished recruitment and is in the follow-up phase. Second trial is INSEMA study, and still accepting recruitments.

Screening and Diagnosis

Dr. Sarah Friedewald made a speech on advances in breast cancer screening and diagnosis. In developed and developing countries, there are recommendations and suggestions about effectiveness of screening programs (16). In the United States, there are different guidelines about starting age of screening suggesting age 40, 45, and age 50. But substantial number of them recommend age 40 to reduce the number of deaths caused by breast cancer. Recent studies demonstrates screening with digital breast tomosynthesis shows decresing recall rates (13%, 7.8%, and 5.9% for 1st, 2nd, and 3rd year screening respectively) when compared to screening with digital mammogrraphy. As there is still no guideline for mammography screening frequency after lumpectomy for breast cancer; due to increased rates of false positive breast biopsies, Dr. Friedewald suggested annualy screening rather than semi-annual screening in this setting. She then presented a population based study titled "Risk of breast cancer after a false positive screening mammogram in relation to mammographic abnormality" from British Columbia with a 11.8 years follow-up. The results showed that women with false positive test almost showed 2 fold incresed relative risk for breast cancer. This statement is important for the follow-up of these patients.

Other

On the 4th day of the conference in general session, Dr. Kuijer from Netherlands presented self-reported 1-year data about risk of arm morbidity after local therapy from the young women's breast cancer study, which is a multicentre prospective cohort conducted in United States. She reported that ALND, increased body-mass index (BMI), less comfortable financial status, and tumour size were associated with increased risk of self-reported arm swelling. Patients with higher BMI and patients treated with mastectomy and RT compared to BCS are more likely to experience decreased range of arm motion.

Dr. Chlebowski underlined the importance of weight loss in postmenopausal patients. They analyzed 61,335 women from the database of Women's Health Initiative Observational study. Dr. Chlebowski and colleagues remarked that overweight women with weight loss of ≥5% were at a lower risk of breast cancer.

Lecture of Dr. Joseph Lo on Prediction of occult invasive disease in ductal carcinoma in situ using deep learning features is probably the most interesting presentation of the 40th SABCS. It gave us a future perspective about what medicine will evolve and what the role of physicians will be. Deep learning is a machine learning algorithm model with many layers to collect and analyze limitless data. In other words, a computer educating itself to diagnose disease. Dr. Lo utilized deep learning features to predict occult invasive disease in DCIS in his study, and achieved reasonable results by this method. However, he concluded that more data input is needed to improve this method.

Conclusion

High-risk breast lesions should be excised if there is a concern that target lesion was not totally or near totally excised in biopsy, if histology demonstrates atypia in presence of a palpable or imaging mass lesion, and if there is a discordant finding.

As multigene tests are becoming more popular, elevated breast cancer risk were established for women with moderate penetrance mutations in selected genes (PALB2, TAM/NBN, CHEK2, etc.).

Success of reoperative SNB (by peritumoral injection) after BCS is significantly higher if patient initially had SNB rather than ALND and did not have RT. Reoperative SNB can also be conducted after recurrences of mastectomy patients by injecting tracers to upper skin flap. In both cases, dual tracer application is recommended. Aberrant lymphatic drainage (internal mammary, contralateral axilla) in 1/3 of the patients should be kept in mind.

Lumpectomy for local recurrence after BCS with RT is feasible if the patient meets the criteria for no RT after surgery.

Intraoperative assesment of sentinel lymph node can be ignored for patients that will probably receive post-mastectomy RT.

To evaluate axillary nodes after NAC, at least 3 or more sentinel node sampling with dual tracer is recommended. If positive axilla after NAC is detected, the standard of care is still performing ALND.

Hormone receptor positive HER2 negative subset is less likely to have positive or high volume nodal disease and less likely to present pathological complete response so that we should consider surgery first if Z0010 and AMAROS eligible.

Recent clinical data suggest that patients with oligometastasis are potentially curable. The concensus about patients most likely to benefit from ablative therapy are patients with long disease-free interval, metastasis of primary breast cancers, small number of metastatic lesions (1-3), small sizes of metastasis, and complete ablation of lesions (R0 resection or other means of complete ablation with different interventions like stereotactic body radiotherapy).

Annualy mammography screening rather than semi-annual screening is recommended after lumpectomy for breast cancer.

Risk of breast cancer after a false positive screening mammogram showed 2-fold increased relative risk.

ALND, increased body-mass index (BMI), less comfortable financial status, and tumour size were associated with increased risk of self-reported arm swelling.

Overweight women with weight loss of ≥5% were at a lower risk of breast cancer.

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Original Article

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Retrospective Analysis of Patients with Synchronous Primary Breast and Thyroid Carcinoma

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ABSTRACT

Objective: Breast and thyroid cancers are commonly encountered malignancies. Increased risk of breast cancer in follow-up period of thyroid cancer or vice versa has been reported. However, they have some associations, synchronous presentation of these tumors is rare. We presented 12 patients diagnosed as breast and thyroid cancer and treated at the same time.

Materials and Methods: Mastectomy and thyroidectomy were performed in 19 patients at the same time. 7 patients were excluded because of benign thyroid pathology. Therefore 12 patients who had diagnosis of synchronous breast and thyroid cancer were included. Data regarding clinical, pathological, treatment and prognostic factors was retrospectively analyzed.

Results: Total thyroidectomy was performed in all patients. The mean age of patients was 54 years (min. 44- max. 70). Only one patient was male. Thyroid pathology was detected preoperatively by FDG PET-CT scan in 11 patients. Breast reconstruction was performed in three patients. The most commonly seen thyroid malignancy was papillary thyroid carcinoma. Postoperative complication rate was 33.3%. Adjuvant chemotherapy was given in 11 patients whereas one patient received adjuvant radiotherapy.

Conclusion: Although synchronous presentation of breast and thyroid cancer is rare, surgical treatment of both of these tumors can be safely performed at the same time. Association of these tumors should be evaluated by large scaled studies.

Keywords: Breast cancer, thyroid cancer, synchronous cancer, mastectomy, thyroidectomy

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Introduction

Breast cancer is the most common cancer in women and it is the second most common cause of death among women due to cancer (1, 2). However, thyroid cancer is projected to be higher than lung, colorectal, and ovarian cancers in near future and estimated to be the third most common cancer of women in USA; it has not been a common cause of death due to cancer (3). 5-year survival rate of thyroid cancer ranges between 95-97% and 5-year survival rate of women with breast cancer is reported 81.9% therefore breast cancer is the determinant for survival in a patient with both breast and thyroid cancer (4, 5).

Both breast and thyroid cancers are frequent among women than men and they both have peak incidence in postmenopausal period (2). This finding, may be coincidence, has lead authors to investigate the association between breast and thyroid cancers. It is believed that they both have some interactions in hormonal and genetic level (6). Increased risk for second primary malignancies after diagnosis of thyroid carcinoma such as salivary gland, small intestine and adrenal gland has been found and this risk increases for breast cancer as the duration of the follow-up is prolonged (7). Although genetic factors, hormones and irradiation have been regarded as risk factors, no absolute relationship has been established yet between them. Either in breast cancer survivors, especially when HER-2 receptor was positive, or in thyroid cancer survivors, increased risk of the other cancer has been found (7, 8). This topic has been investigated by cohort and case-control studies in survivors butfew studies presented patients diagnosed synchronously and treated at the same time (9, 10).

In this study, we present patients who were diagnosed preoperatively as synchronous breast cancer and thyroid pathology and underwent mastectomy and thyroidectomy at the same session.

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Materials and Methods

In total, 1297 thyroidectomies and 1210 mastectomies were performed between November 2011 and January 2016 at our institute. Data of patients were retrospectively collected via patient records. Among these patients, both mastectomy and thyroidectomy were performed in 19 patients. A total of 729 patients with diagnosis of thyroid cancer and 579 patients with diagnosis of breast cancer were found. 12 patients had diagnosis of synchronous breast and thyroid cancer, whereas 7 patients had breast cancer and benign thyroid disease.

Characteristics of patients, pathological characteristics of both cancers, neoadjuvant or adjuvant chemoradiotherapy status, postoperative radioiodine ablation therapy status, postoperative complications, recurrence, survival, disease-free survival and follow-up of the patients are given in Table 1 and 2. This study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration.

Statistical Packages for the Social Sciences (SPSS) software package was used for statistical analysis version 17.0 (SPSS Inc., Chicago, IL, USA). If continuous variables were normal, they were described as the mean±standard deviation ($p>0.05$ in Kolmogorov-Smirnov test or Shapira-Wilk ($n<30$)), and if the continuous variables were not normal, they were described as the median.

Results

A total of 12 mastectomies and thyroidectomies were performed simultaneouly in patients with preoperative diagnosis of breast cancer and thyroid pathology. Mean age of patients was 54 years (min. 44-max. 70). Only 1 (8.3%) patient was male. Half of the patients had preoperative thyroid fine needle aspiration with diagnosis of 3 malignant cytology, 2 Hurthle cell neoplasia and 1 follicular neoplasia. Other 6 patients had either hyperthyroidism or thyroid nodule larger than 3 cm. on physical examination and ultrasound.

11 (91.7%) patients had preoperative FDG PET-CT scan and thyroid pathology was detected in all of them. In all 12 patients, primary complaint of the patient was lump or swelling in the breast therefore none of the patients presented with primary thyroid pathology. Thyroid patholgy was detected on FDG PET-CT scan or physical examination. Total thyroidectomy was performed in all patients. Only 1 (8.3%) patient had papillary thyroid lymph node metastasis in the follow-up period and modified radical lymph node dissection was performed. (Table 3) shows the details of breast surgeries performed in all cases. Immediate breast reconstruction type was silicone implantation and

Table 1. Characteristics of patients according to breast pathology

Patient no.	Age	Sex	Operation	BC histology	BC TNM#	ER/PR**	Neoadjuvant therapy	Adjuvant therapy
1	53	F	SM+ALND+TT	Invasive DC+DCIS	T2N1M0	60-70/5	None	AC+DT+Tamoxifen RT (66Gy)
2	50	F	MRM+IBR+TT	Invasive LC+DCIS	T2N2M0	60-70/60-70	None	AC+DT+TZM RT(50Gy)
3	49	F	SM+SLND+IBR+TT	Invasive DC+DCIS	T1cN0M0	Neg/Neg	None	Unknown regimen*
4	48	F	MRM+TT	Invasive BC	TXN2M0/T0N0M0	95/70	AC+DT+TZM	TZM RT (50Gy)
5	44	F	SM+SLND+TT	Invasive DC+DCIS	T1cN0M0	85/95	None	AC+Tamoxifen
6	63	F	MRM+TT	Invasive DC+DCIS	T2N1aM0	Neg/Neg	None	AC+TZM+ Tamoxifen
7	53	M	SiM+SLND+TT	Invasive DC+DCIS	T1cN0M0	90-95/30-40	None	Unknown regimen*
8	50	F	MRM+TT	Mixed carcinoma+DCIS	T2N3aM0	100/70	None	AC+DT RT(50Gy)
9	53	F	SM+SLND+TT	Invasive DC	T2N1M0	Neg/Neg	None	CEF+DT RT(50.4Gy)
10	70	F	MRM+TT	Invasive DC+DCIS	T2N2aM0	90-95/15-20	None	CEF+DT RT (50.4Gy)
11	62	F	SM+SLND+TT	Invasive DC+DCIS	T1cN0M0	90-95/10-15	None	RT (50.4Gy)
12	53	F	MRM+DBRi+TT	Invasive DC+DCIS	T2N3M0	Neg/Neg	None	CEF+DT+TZM RT(50Gy)

*: Adjuvant chemoradiotherapy given in another hospital.
**: Estrogen or progesteron receptor percentage.
#: Preoperative clinical and postoperative pathological TNM stage (Clinical TNM stage before neoadjuvant therapy and postoperative pathological TNM stage was both given for patient number 4)
AC: adriamycin+cyclophosphamide; ALND: axillary lymph node dissection; BC: breast cancer; CEF: Cyclophosphamide+Epirubicin+Flourouracil; DBRi: delayed breast reconstruction with implantation; DC: ductal carcinoma; DCIS: ductal carcinoma insitu; DT: docetaxel; ER: estrogen receptor; F: female; IBR: immediate breast reconstruction; LC: lobular carcinoma; M: male, MRM: modified radical mastectomy; PR: progesterone receptor; SM: simple mastectomy; SLND: sentinel lymph node dissection; SM: segmental mastectomy; RT: radiotherapy; TT: total thyroidectomy; TZM: trastuzumab

Table 2. Characteristics of patients according to thyroid cancer, survival and complications

Patient no.	Age	Sex	TC histology	TC size (mm)	RIA (mci)	Disease free survival (Months)	Follow-up (Months)	Postoperative Complication
1	53	F	PC	20	150	29	32	Re-exicision (Breast)
2	50	F	PC	15	None	22	22	SSI
3	49	F	PC	6	UR	12	12	None
4	48	F	PC	8	None	22	22	None
5	44	F	PC	17	100	14	14	None
6	63	F	PC	7	None	30	30	None
7	53	M	PC	6	UR	9	9	None
8	50	F	PC	2	None	12	12	Seroma
9	53	F	FC	20	100	8	8	None
10	70	F	PC	2	None	8	8	None
11	62	F	PC	1	None	4	4	None
12	53	F	PC	30	100	15	15	None

FC: follicular carcinoma; F: female, M: male; PC: papillary carcinoma; RIA: radioactive iodine ablation; SSI: surgical site infection; TC: thyroid cancer; UR: unknown regimen

Table 3. Breast surgery type which was performed for patients

Surgery type	Number of patients
MRM	4
SM+sLND	4
SM+aLND	1
SM+aLND+IBR	1
Simple mastectomy+sLND	1
MRM+IBR	1
MRM+DBR	1

aLND: axillary lymph node dissection; DBR: delayed breast reconstruction; IBR: immediate breast reconstruction; MRM: modified radical mastectomy; sLND: sentinel lymph node dissection; SM: segmental mastectomy

delayed breast reconstruction type was tissue expander and silicone implant.

Only 1 (8.3%) patient who underwent simple mastectomy (SM) with axillary lymph node dissection (LND) had positive surgical margins and reoperation with wide surgical resection was performed for this patient.

Histopathological findings

8 (66.8%) invasive ductal breast carcinoma + ductal carcinoma in situ and papillary thyroid carcinoma, 1 (8.3%) invasive lobular breast carcinoma + ductal carcinoma in situ and papillary thyroid carcinoma, 1 (8.3%) invasive breast carcinoma and papillary thyroid carcinoma, 1 (8.3%) mixed (invasive ductal and invasive mucinous) breast carcinoma + ductal carcinoma in situ and papillary thyroid carcinoma and 1 (8.3%) invasive ductal breast carcinoma and follicular thyroid carcinoma.

Treatment details

8 (66.8%) patients received adjuvant chemotherapy and radiotherapy, 1 (8.3%) patient received neoadjuvant and adjuvant chemotherapy and radiotherapy, 2 (16.6%) patients received adjuvant chemotherapy only and 1 (8.3%) patient received radiotherapy only. Only half of the patients (50%) received radioiodine ablation therapy.

Postoperative complications

Postoperative complications were due to mastectomy. The overall complication rate was 16.7%. These complications were seroma in 1 patient and wound infection in 1 patient, who were treated by conservative management. Average disease-free survival was 15.4 months (range between 4-30 months). Mean follow-up was 15.6 months (range between 4-32 months). No mortality was observed in the follow-up period.

Discussion and Conclusion

Breast cancer is the most common malignancy in women around the world. The 5-year relative survival rate of this cancer improved recently due to early detection and advances in treatment (11). As survival rates and incidence of this cancer has increased, the number of breast cancer survivors has also increased. During the diagnosis of breast cancer patients, detection of second primary malignancy is a significant issue.

Warren et al. (12) described synchronous primary cancers as a tumor diagnosed simultaneously with breast cancer or within a time interval of 6 months. The most common synchronous malignancy of breast cancer is thyroid cancer or vise versa (9, 13). There is an increased risk of secondary malignancy for breast or thyroid cancer survivors (14). Many studies have suggested that there is an association between thyroid diseases and breast carcinoma (15) whereas some authors did not find any obvious association (16).

The interactions between thyroid and breast disorders are based on hormonal and cellular receptor mechanisms (17, 18). In a recent prospective study, although no statistical difference was observed, thyroglobuline gene polymorphism and autoimmune thyroid disease was found to have high prevelance among breast cancer patients (19). Thyroid cancer survivors also have been found to develop breast cancer early, have more estrogen and progesterone receptor positive tumors, and have a greater incidence of mixed invasive cancer (20). Estrogen receptors have been found in thyroid tissue (21). Estrogen was found to have an influence on thyroid glands (22). The histology of the breast cancer that develops after thyroid cancer is different than the general population, with a greater percentage of mixed ductal and lobular invasive cancer and a greater percentage of ER/PR-positive tumors (20). In this current study, we found high percentage of ER/PR positive tumors (66.6%). Although indicated by many studies, an association between breast and thyroid cancer still remains controversial. All these studies suggest a possible interaction among breast and thyroid cancers.

The first malignancy diagnosed in our patients was breast cancer. Thyroid pathology was diagnosed either on physical examination or preoperative evaluation of breast cancer with FDG PET-CT scan. FDG PET-CT scan has been widely used for the diagnosis, initial staging, restaging, early treatment response assessment and evaluation of metastatic disease response of breast cancer (23). Although it has some disadvantages like irradiation, it is useful for detecting metastasis of breast cancer. It is reported to have a negative predictive value of 90 % for detection of thyroid nodules (24). It also detected 91.7 % of patients with thyroid pathology in our study.

Thyroid hormones have been found to stimulate cell proliferation in breast tissue, enhance the estradiol-mediated effects on cell proliferation, promote growth and induce the expression of progesterone receptors by mimicing the effects of estradiol (25, 26). Thyroid receptors found to be located in both normal and malignant breast cells (27). In a recent study, high free T4 levels and thyroid peroxidase antibody (TPO-Ab) levels were found to be associated with an increased risk of breast cancer (28). In a meta-analysis including 8 cross-sectional studies, authors found serum levels of free T3, TPO-Ab and thyroglobulin antibody to be significantly higher in patients with breast cancer than in healthy controls (29). Therefore, there is great evidence that the breast and thyroid tissue has some interactions on hormonal basis mainly influenced by the hormones secreted from thyroid gland. Thyroid receptors (TR) are encoded by two genes, TRα and TRβ, which are located on human chromosomes 17 and 3, respectively. In a recent study performed among Chinese people, aberrant expression and mutations of the TRβ1 gene were found to be associated with the development of breast cancer (30). Thus, thyroid hormone receptors play a role in breast cancer development.

Although the most common thyroid cancer type found to be associated with breast cancer is papillary thyroid cancer (85.9%), follicular cancer (11%) is also found to be increased in frequency (20). In our study, papillary thyroid cancer (91.7%) is also found to be the most common histologic type together with breast cancer whereas follicular cancer incidence was found as 8.3%.

In this current study we performed both mastectomy and thyroidectomy at the same time. Although our study has a limitation with short follow-up period, the main determinant of patients with synchronous breast and thyroid cancer is the breast cancer because of shorter survival rates. Performing mastectomy first and then thyroidectomy in the follow-up period may result in delay of the chemotherapy and radiotherapy. We believe that these two operations can be safely performed simultaneously as thyroidectomy adds only 60 minutes to the overall operation time, so it does not increase the risk for peroperative or postoperative complications due to anesthesia. Adjuvant radiotherapy for breast cancer reported to have some influence on thyroid tissue leading to hypothyroidism (31). Radiation is also known to increase risk for thyroid malignancy. Thus, it is better to diagnose thyroid pathology before breast cancer treatment and preoperative assesment of thyroid gland in patients diagnosed with breast cancer is crucial.

These different findings from literature represents one of the limitation of our study which was the result of small patient population. Retrospective design of this study is another limitation.

Although the exact mechanism of association between breast and thyroid cancers still remains unknown, synchronous presentation of these tumors can be seen. Thus, preoperative assesment of thyroid gland by physical examination is mandatory in patients diagnosed with breast cancer and if these patients are clinically negative for thyroid pathology radiological evaluation can be performed for them. Treatment for both of these cancers can be safely performed at the same time.

Ethics Committee Approval: Ethics committee approval was not taken due to retrospective design of the study.

Informed Consent: Informed consent was not taken due to retrospective design of the study.

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Original Article

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Dual-Phase ADC Modelling of Breast Masses in Diffusion-Weighted Imaging: Comparison with Histopathologic Findings

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ABSTRACT

Objective: To investigate the diagnostic value of dual-phase apparent diffusion coefficient (ADC) compared to traditional ADC values in quantitative diffusion-weighted imaging (DWI) for differentiating between benign and malignant breast masses.

Materials and Methods: Diffusion-weighted images of pathologically confirmed 88 benign and 85 malignant lesions acquired using a 3.0T MR scanner were analyzed. Small region-of-interests focusing on the highest signal intensity of lesions were used. Lesion ADC estimates were obtained separately from all b-value images (ADC; b=50, 400 and 800s/mm^2), lower b-value images (ADC_{low}; b=50 and 400s/mm^2) and higher b-value images (ADC_{high}; b=400 and 800s/mm^2). A set of dual-phase ADC (dpADC) models were constructed using ADC_{low}, ADC_{high} and a perfusion influence factor ranging from 0 to 1.

Results: Strong positive correlation is observable between ADC and all dpADCs (ρ=0.80-1.00). Differences in ADC and dpADCs between the benign and the malignant lesions are all significant ($p<0.05$). In detecting malignancy, traditional lesion ADC provides a good performance (AUC=89.9%) however $dpADC_{0.5}$ (dpADC with a factor of 0.5) accomplishes a better performance (AUC=90.8%). At optimal thresholds, ADC achieves 94.1% sensitivity, 72.7% specificity and 83.2% accuracy while $dpADC_{0.5}$ leads to 92.9% sensitivity, 79.5% specificity and 86.1% accuracy.

Conclusion: Dual-phase ADC modelling may improve the accuracy in breast cancer diagnosis using DWI. Further prospective studies are needed to justify its benefit in clinical setting.

Keywords: Breast, diffusion-weighted imaging, apparent diffusion coefficient, dual-phase

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Introduction

Diffusion-weighted imaging (DWI) utilizes diffusion signal attenuated due to the random microscopic motion of water molecules influenced by cell density, membrane integrity, tissue microstructure, perfusion and diffusion heterogeneity within the tissue (1). When compared with benign lesions and healthy tissue, more restricted water mobility of malignant lesions engenders slower attenuation of the diffusion signal captured from a set of images acquired with different degrees of diffusion weighting (reported as b-value) (2).

Quantitative diagnosis of cancer from DWI relies on metrics computed as the parameters of a "signal attenuation" model fitted to the diffusion signal data. The need for reliable and precise metrics motivates new studies on development of advanced models for better fittings to the diffusion signal data or advanced methods for optimized estimation of diffusion metrics (3). There exist several advanced exponential signal attenuation models such as stretched exponential (4), bi-exponential (known as intravoxel incoherent motion) (5), statistical (6) and kurtosis (7) capable of describing complex diffusion processes of the breast tissue. However, the parameters derived from these models are difficult to estimate and quite complex for use in diagnosis. For instance, physiological basis of the heterogeneity index of the stretched exponential model is reported to be uncertain and likewise pseudo-diffusion coefficient of the biexponential model is thought to be unreliable (8). On the other hand, these models involve several parameters that complicate both the diffusion estimation process and the diffusion weighted imaging protocol. To get accurate diffusion estimates, the initial value and the limits for any model parameter should be determined very carefully and an appropriate optimization method should be employed (9). To reach consistent numerical solutions, the number of b-values of the diffusion weighted imaging protocol must set to be more than the number of parameters in the model and

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large number of b-values would lengthen the imaging time remarkably making it unmanageable in clinical practice. These challenges promote the use of a mono-exponential model, that offers only one free parameter (namely apparent diffusion coefficient) estimated from two different b-value images with simplicity and high reproducibility, as the traditional model in diagnostic DWI in clinical practice (10).

Diffusion-weighted imaging and the use of apparent diffusion coefficient has been reported to be a very beneficial technique adjunct to dynamic contrast-enhanced imaging in diagnosis of breast cancer using magnetic resonance (MR) imaging (11, 12). While DWI holds potential to improve the detection and biological characterization of breast cancer (13), apparent diffusion coefficient (ADC) is capable of reflecting breast tissue cellularity, fluid viscosity, membrane permeability, macromolecular structures, microvascularity and lesion blood flow (14). Benign lesions have higher ADC than malignant lesions, especially the invasive carcinomas mainly due to their less compact cellularity (15). However, overlap between the ADC estimates from benign and malignant breast lesions motivate new studies to improve the performance of ADC in distinguishing benign lesions from malignant lesions.

The b-value set used during diffusion weighted imaging has an impact on the fitting performance of the mono-exponential model and on the diagnostic performance of ADC consequently (16). The lowest b-value is set to be sufficiently high so as the model can describe the diffusion signal data appropriately ($b \geq 50 s/mm^2$ is usually used) while the highest b-value should be chosen so as to provide adequate suppression of water signal from normal fibroglandular tissue and maximum breast lesion visibility (17) (The use of $b \geq 800 s/mm^2$ is usually recommended (18, 19)). Incorporating more than two b-values into the imaging protocol has been reported to provide more precise sampling of the diffusion signal and consistent ADC estimates (20, 21).

Diagnostic performance of ADC is also influenced by the methods used during image analysis and computation. A smaller region-of-interest (ROI) focusing on the highest signal intensity for the lesion is reported to have a better differential value for ADC when compared with a larger ROI for the overall lesion, especially in discrimination of invasive carcinomas (22). Normalized ADC (also called ADC ratio) calculated from the ratio of the lesion ADC to a reference tissue ADC (usually ipsilateral glandular breast tissue) is illustrated to make some improvements in the overall performance of ADC (23-25). Two separate ADCs from a lesion, one estimated from low b-value images and the other estimated from high b-value images, are demonstrated to be potentially more useful than a single lesion ADC in assessing the non-Gaussian water diffusion in vivo that is more closely related to the advanced models (26). In this study, we introduce dual-phase ADC modelling that integrates two separate ADCs, one from low b-value images and the other from high b-value images, and evaluate the utility of the modeling for breast masses in comparison with the histopathologic findings in quantitative DWI.

Materials and Methods

Patient Population

A total of one hundred seventy-three lesions (88 benign and 85 malignant) from 173 women aged 18-78 years (mean, 46 years), who underwent standard breast MRI including diffusion weighted imaging to clarify uncertain clinical, mammographic, sonographic findings or to assess preoperative staging of patients with known malignancies, have been retrospectively enrolled in this study. Written informed consent was obtained from each woman and local ethics committee approval was received. All findings were verified by histopathological examination. Average lesion size was 18.2±8.1mm. The benign lesions were 45 fibroadenomas, 14 columnar cell changes, 8 fibroses, 6 adenoses, 5 abscesses, 5 apocrine metaplasias and 5 other benign changes. The malignant lesions were 61 invasive ductal carcinomas, 9 invasive lobular carcinomas, 8 ductal carcinomas *in situ*, 3 invasive mucinous carcinomas, 1 invasive apocrine carcinoma, 1 medullary carcinoma, 1 medullary like carcinoma and 1 liposarcoma.

Breast MR Imaging Protocol

Breast MR imaging was performed by a 3T MR scanner (Magnetom Verio, Siemens Healthcare, Erlangen, Germany) using a dedicated 16-channel breast coil while patients were lying in prone position. At first, T2-weighted images were acquired using an axial turbo spin-echo with 70ms echo time (TE), 4100ms repetition time (TR), 448×381 matrix size, 320mm field of view (FOV), 3mm slice thickness. Next, diffusion-weighted images were captured in the axial plane using a 2D spin-echo echo-planar imaging (EPI) sequence at three b-values (b=50, 400 and $800 s/mm^2$) with the following parameters: 86ms echo time, 9700ms repetition time, 90° flip angle, 3 averages, 82×192 matrix size, 155×360mm FOV and 4mm slice thickness (leading to an in-plane resolution of $1.9 \times 1.9 \times 4 mm^3$). Finally, axial dynamic contrast-enhanced MR images were taken using 3D volumetric interpolated breath-hold (VIBE) imaging sequence with the following parameters: 1.77ms echo time, 5.01ms repetition time, 10° flip angle, 512×512 matrix size, 340mm FOV and 1mm slice thickness. During and immediately after the bolus injection of contrast agent Gadobutrol (0.1mmol/kg Gadovist®, Bayer Schering Pharma, Berlin, Germany) or Gadoterate Meglumine (0.1mmol/kg Dotarem®, Guerbet, Villepinte, France), one pre-contrast and six postcontrast bilateral images were acquired with a temporal resolution of 88 seconds.

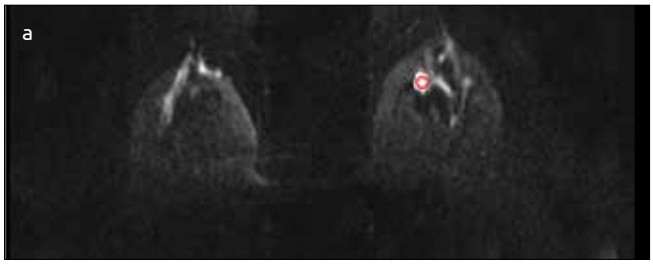
Image Evaluation and ROI Delineation

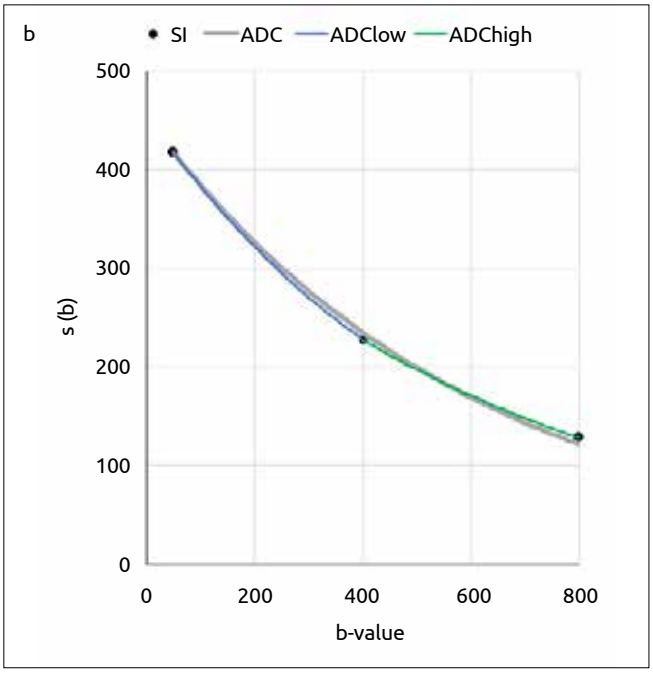
All images acquired during imaging were transferred to workstation and evaluated by two experienced radiologists (with 4 and 17 years of experience in breast MRI, respectively) using Syngo. Via 3D reading and advanced visualization software (Siemens Healthcare, Erlangen, Germany) installed on the workstation. Both radiologists were blinded to pathology during evaluation. The radiologists first analyzed the dynamic contrast-enhanced images to localize lesions. The radiologists next evaluated each localized lesion on diffusion-weighted images and manually placed a region of interest (ROI) with consensus on the diffusion-weighted image with $b=800 s/mm^2$ with care to include only the solid portion of the lesion with the highest signal intensity, excluding the necrotic and the cystic regions. All ROIs were defined to be circular with a diameter of 5mm. For each ROI placed, average signal intensity for each b-value of the diffusion-weighted imaging protocol given by the software was recorded for use to estimate apparent diffusion coefficients.

Dual-phase Apparent Diffusion Coefficient Modelling

Dual-phase ADC modelling integrates the two ADC estimates: ADC_{low} from lower b-value images ($b=50\text{-}400 s/mm^2$) and ADC_{high} from higher b-value images ($b=400\text{-}800 s/mm^2$) by using the following formula introduced in this study:

$$dpADC_{pf} = pf \times ADC_{low} + (1 - pf) \times ADC_{high} \quad (1)$$





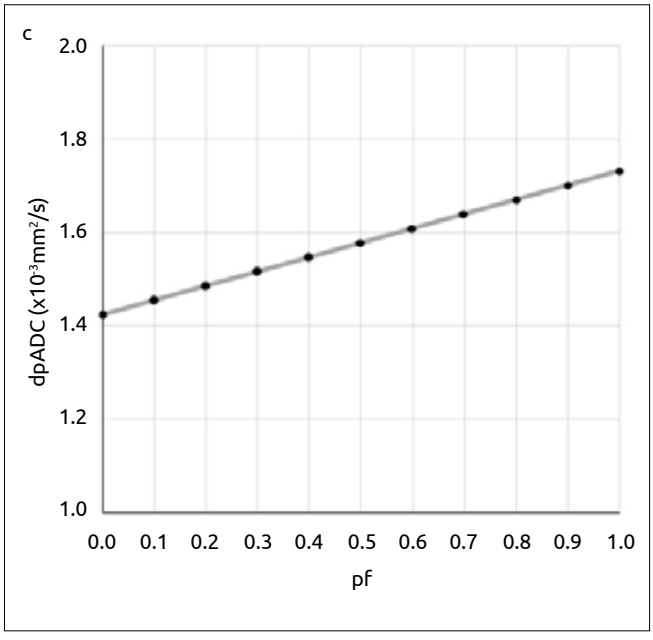


Figure 1. a-c. A 48-year-old woman with a benign lesion (a fibroadenoma) finding on the left breast and (a) the ROI placed for the lesion (solid red line contour) on the diffusion-weighted image at b=800mm^2/s. (b) Plots for the average signal intensity measurements recorded and for the results of the nonlinear fittings obtained (ADC=1.64×10^{-3}mm^2/s, ADC_{low}=1.73×10^{-3}mm^2/s and ADC_{high}=1.42×10^{-3}mm^2/s) and (c) Plot for the dpADC computed for a specific "perfusion" influence factor

Here pf is "perfusion" influence factor that ranges from 0 to 1. When pf is set to 0, the influence of ADC_{low} is omitted giving $dpADC_0$ = ADC_{high}. In contrast, if pf is set to 1, the influence of ADC_{high} is omitted and $dpADC_{1.0}$=ADC_{low}. ADC_{low} is influenced by perfusion mostly and diffusion in a certain degree while ADC_{high} reflects diffusion only. By voluntarily modifying the value of pf, different dual-phase ADC models can be obtained. The apparent diffusion coefficient can be estimated by using the mono-exponential model and the average signal intensity for an ROI recorded for n-th b-value of the diffusion-weighted image, $S(b_n)$:

$$S(b_n) = S(b_1) \times \exp^{-b_n \times ADC} \quad (2)$$

In this study, ADC estimates were obtained for all breast lesions separately by using average signal intensity values from all b-value images (ADC; b=50, 400 and 800s/mm^2), from only lower b-value images (ADC_{low}; b=50 and 400s/mm^2) and from only higher b-value images (ADC_{high}; b=400 and 800s/mm^2). The estimations were performed using our own in-house developed computer software based on MatLab (Mathworks, Natick, MA) implementing a nonlinear fitting method based on the Trust-Region-Reflective least squares algorithm with the same pre-set initial value and the same limits for the ADC parameter (initial value=1.5×10^{-3}mm^2/s, upper and lower limits=3.0×10^{-3}mm^2/s and 0.3×10^{-3}mm^2/s, respectively) (Figure 1).

Statistical Analysis

Systematic difference in ADC and dpADC of the lesions were tested using Wilcoxon signed-ranks test. Spearman's rho (ρ) was used to test correlation between lesion dpADC and lesion ADC. Absolute relative difference between dpADC and ADC was measured using

$$\Delta_{rel} = \frac{|dpADC - ADC|}{ADC} \times 100 \quad (3)$$

Systematic differences in ADC and dpADC between benign and malignant lesions were tested using Mann-Whitney U-test. Diagnostic performance was assessed by plotting the receiver operating characteristic (ROC) curves and calculating the areas under the ROC curves (AUC). A p value of <0.05 was considered to be statistically significant.

Optimal thresholds for ADC and dpADC were determined by applying Youden statistics to the results of ROC analysis while considering improvements in both sensitivity and specificity. The classification performances of the optimal thresholds were assessed using sensitivity (Se), specificity (Sp), positive predictive value (PPV) and accuracy (Ac). All statistical analyses were performed using SPSS software for Windows (version 23; SPSS, Chicago, IL).

Results

Dual-phase apparent diffusion coefficient models using a set of perfusion influence factor (pf) and overall dual-phase ADC values (dpADC) estimated by the models from all breast lesions enrolled in this study are seen in Table 1. dpADC is at its minimum when pf is set to zero while dpADC is at its maximum when pf is set to one showing that dpADC is directly proportional to the perfusion influence factor: an increase in the factor leads to an increase in dpADC. ADC estimate from all lesions is 1.47±0.51×10^{-3}mm^2/s and a very similar value of 1.47±0.52×10^{-3}mm^2/s is obtained by the dpADC model with a pf of 0.7 leading to the lowest absolute relative difference among all the dpADC models studied (Δ_{rel}=1.6%). However, there are systematic difference in ADC and dpADC from all the models, but significant positive correlations are present between ADC and dpADC at all (p<0.05). Strong correlations exist between ADC and dpADC

obtained by the models using pf values of 0, 0.1 and 0.2 (ρ=0.80-0.90) but the rest of the models offer very strong correlations (ρ=0.90-1.00) (Figure 2). Table 2 shows the ADC and dpADC estimates from the benign and the malignant lesions. Independent of the perfusion influence fraction considered during modelling, low dpADC values indicate malignancy as in traditional ADC case. The differences in dpADC estimates between benign and malignant lesions from all the models are significant (p<0.05).

Table 1. Dual-phase ADC models and lesion dpADC with respect to perfusion influence factor and corresponding correlations and relative differences between dpADC and ADC

Model	pf	dpADC	ρ	Mean Δ_{rel}(%)
$dpADC_0$	0	1.31±0.61	0.80	20.4
$dpADC_{0.1}$	0.1	1.33±0.58	0.85	17.4
$dpADC_{0.2}$	0.2	1.36±0.56	0.88	14.3
$dpADC_{0.3}$	0.3	1.38±0.54	0.93	11.3
$dpADC_{0.4}$	0.4	1.40±0.52	0.96	8.2
$dpADC_{0.5}$	0.5	1.43±0.51	0.99	5.2
$dpADC_{0.6}$	0.6	1.45±0.51	1.00	2.1
$dpADC_{0.7}$	0.7	1.47±0.51	1.00	1.6
$dpADC_{0.8}$	0.8	1.49±0.52	0.99	4.0
$dpADC_{0.9}$	0.9	1.52±0.53	0.97	7.1
$dpADC_{1.0}$	1.0	1.54±0.55	0.94	10.1

Mean±SD in $10^{-3}mm^2/s$, overall ADC is (1.47 0.52)x$10^{-3}mm^2/s$
All statistical values are significant (p<0.05)
pf: perfusion influence factor; dpADC: dual-phase ADC; ρ: spearman's rho; Δ_{rel}: absolute relative difference

Table 2. Benign and malignant lesion dpADCs

Model	Benign Lesion	Malignant Lesion
$dpADC_0$	1.68±0.56 [a]	0.92±0.38
$dpADC_{0.1}$	1.70±0.52	0.95±0.35
$dpADC_{0.2}$	1.72±0.49	0.98±0.33
$dpADC_{0.3}$	1.73±0.46	1.00±0.31
$dpADC_{0.4}$	1.75±0.45	1.04±0.30
$dpADC_{0.5}$	1.76±0.44	1.07±0.30
$dpADC_{0.6}$	1.78±0.43	1.10±0.30
$dpADC_{0.7}$	1.80±0.44	1.13±0.32
$dpADC_{0.8}$	1.81±0.45	1.16±0.34
$dpADC_{0.9}$	1.83±0.48	1.19±0.34
$dpADC_{1.0}$	1.84±0.51	1.23±0.40

[a]Mean±SD in $10^{-3}mm^2/s$
All statistical values are significant (p<0.05)
dpADC: dual-phase ADC; ADC: apparent diffusion coefficient

Results of the ROC analyses of ADC and dpADC in differentiation of malignant lesions from benign lesions are as presented in Table 3. The dpADC models using a pf value of 0.2, 0.3, 0.4, 0.5 or 0.6 provides better performance (AUC≥90.0%) when compared to ADC (AUC=89.9%). Among these models, the model $dpADC_{0.5}$ that en-

Table 3. Diagnostic performance of dpADC and of ADC (in %)

			95% Confidence Interval of AUC	
	AUC	SE	Lower Bound	Upper Bound
$dpADC_{0.5}$	90.8	2.2	86.4	95.2
$dpADC_{0.4}$	90.7	2.3	86.3	95.2
$dpADC_{0.3}$	90.6	2.3	86.2	95.1
$dpADC_{0.6}$	90.3	2.3	85.7	94.8
$dpADC_{0.2}$	90.0	2.4	85.3	94.7
ADC	89.9	2.4	85.3	94.5
$dpADC_{0.7}$	89.7	2.4	85.0	94.3
$dpADC_{0.1}$	89.1	2.5	84.2	94.0
$dpADC_0$	88.1	2.6	82.9	89.9
$dpADC_{0.8}$	88.0	2.5	83.0	93.2
$dpADC_{0.9}$	86.2	2.7	80.8	91.5
$dpADC_{1.0}$	84.1	3.0	78.3	89.9

ADC: apparent diffusion coefficient; dpADC: dual-phase ADC; AUC: area under the curve; SE: standard error

Table 4. Classification performance of dpADC and of ADC

	Threshold[a]	False Detections	Se	Sp	PPV	Ac
$dpADC_{0.5}$	1.50	24 [18[b]+6[b]]	92.9	79.5	81.4	86.1
$dpADC_{0.6}$	1.54	25 [19+6]	92.9	78.4	80.6	85.5
$dpADC_{0.2}$	1.29	26 [14+12]	85.9	84.1	83.9	85.0
$dpADC_{0.3}$	1.33	26 [14+12]	85.9	84.1	83.9	85.0
$dpADC_{0.4}$	1.44	26 [18+8]	90.6	79.5	81.1	85.0
$dpADC_{0.1}$	1.35	28 [10+18]	88.2	79.5	80.6	83.8
ADC	1.61	29 [24+5]	94.1	72.7	76.9	83.2
$dpADC_{0.7}$	1.53	29 [12+17]	85.9	80.7	81.1	83.2
$dpADC_0$	1.13	30 [19+11]	77.6	87.5	85.7	82.7
$dpADC_{0.8}$	1.40	33 [18+15]	78.8	83.0	81.7	80.9
$dpADC_{0.9}$	1.42	35 [21+14]	75.3	84.1	82.1	79.8
$dpADC_{1.0}$	1.47	37 [21+16]	75.3	81.8	80	78.6

[a]In 10^{-3} mm^2/s
[b]Number of false positives and cNumber of false negatives
ADC: apparent diffusion coefficient; dpADC: dual-phase ADC; Se: sensitivity; Sp: specificity; PPV: positive predictive value; Ac: accuracy

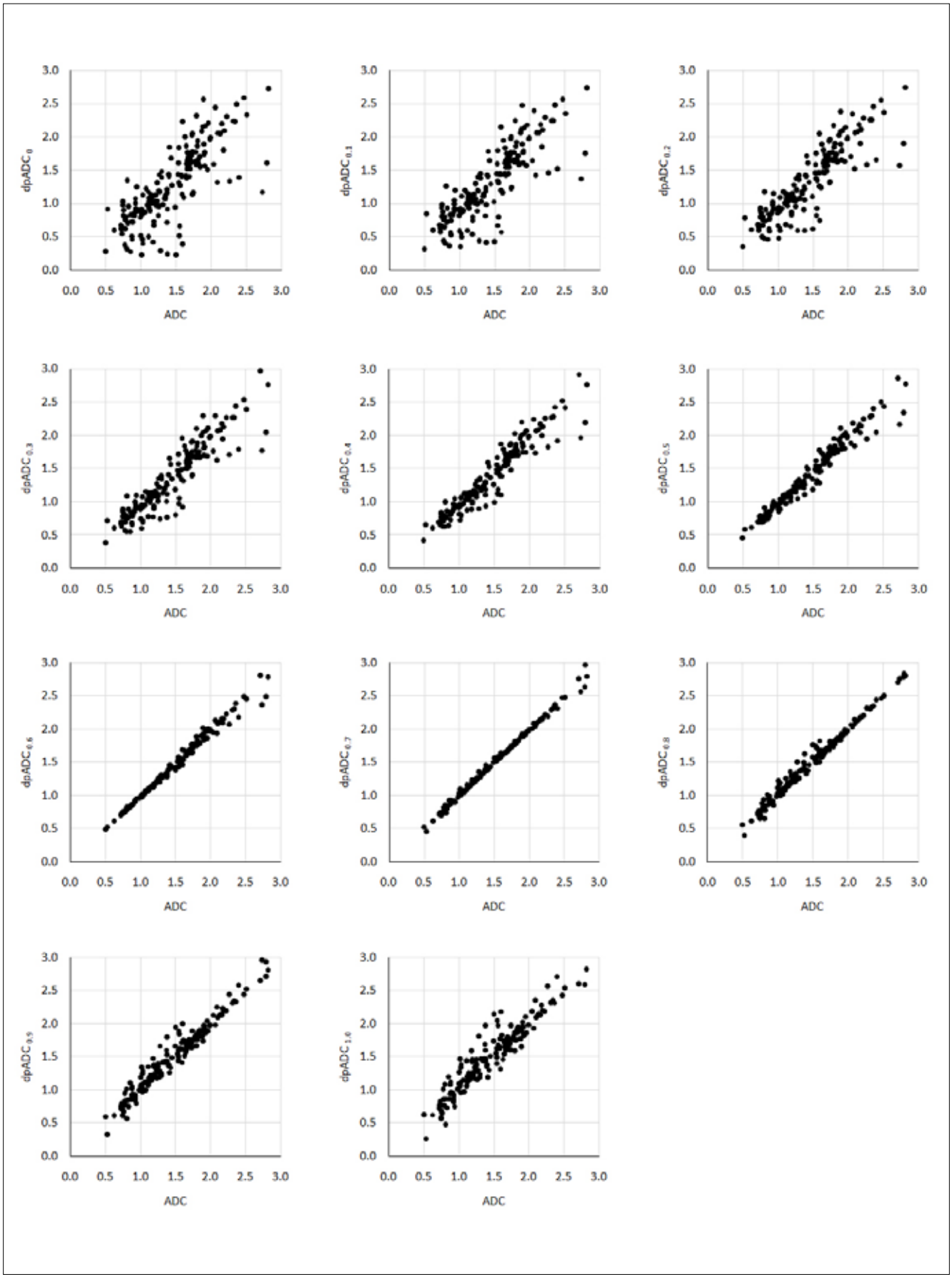


Figure 2. Plots for the ADC estimates with respect to dpADC estimates by the model using a pf of (a) 0, (b) 0.1, (c) 0.2, (d) 0.3, (e) 0.4, (f) 0.5, (g) 0.6, (h) 0.7, (i) 0.8, (j) 0.9 and (k) 1.0 from all lesions

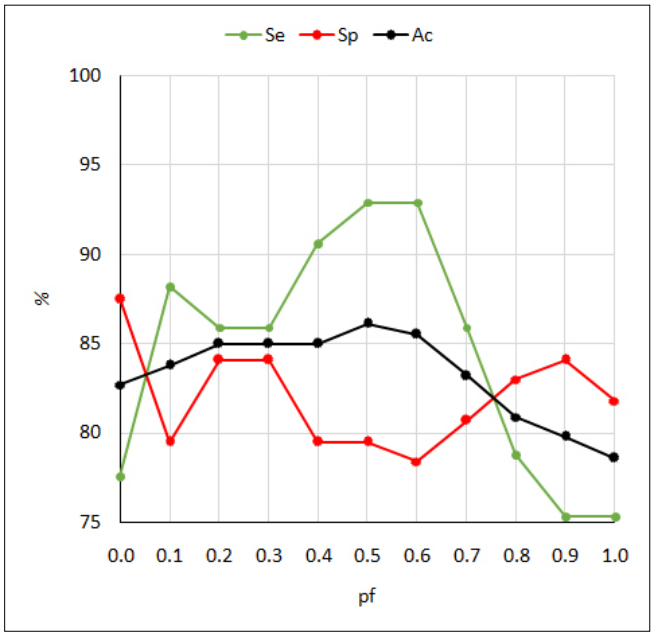


Figure 3. Plots for the sensitivity, specificity and overall accuracy of the dpADC models

rolls a perfusion influence fraction of 0.5 stands out in terms of its highest diagnostic accuracy (AUC=90.8%).

Diagnostic performances of ADC and dpADC form the models for optimal thresholds determined are listed in Table 4 and the corresponding plots for sensitivity, specificity and accuracy of the models are seen in Figure 3. ADC achieves 94.1% sensitivity, 72.7% specificity, 76.9% positive predictive value and 83.2% accuracy due to 5 false-negative and 24 false-positive detections (29 false detections in total) at an optimal threshold of $1.61\times10^{-3}mm^2/s$. Among the dpADC models, $dpADC_0$ offers low sensitivity (77.6%) but the highest specificity (87.5%) meanwhile $dpADC_{0.5}$ and $dpADC_{0.6}$ provide the highest sensitivity (92.9%) but lower specificities (79.5% and 78.4%, respectively). However, the best performance is given by $dpADC_{0.5}$: 92.9% sensitivity, 79.5% specificity, 81.4% positive predictive value and 86.1% accuracy due to 6 false-negative and 18 false-positive detections (24 false detections in total) at an optimal threshold of $1.50\times10^{-3}mm^2/s$. These results show that when compared to ADC, dual-phase ADC can provide almost the same sensitivity but considerably higher specificity that improves the positive predictive value and the accuracy.

Discussion and Conclusion

Challenges in quantitative diagnosis of breast cancer from diffusion-weighted imaging (DWI) motivate new studies to develop enhanced methods focusing on better modelling of the diffusion signal data and on enhancing the diagnostic performance of diffusion coefficients from the models. This study introduces a dual-phase apparent diffusion coefficient modeling that may improve the dialogistic performance of traditional ADC in breast cancer.

The dual-phase apparent diffusion coefficient model integrates two separate ADCs: one from low b-value images ($b=50\text{-}400s/mm^2$) and the other from high b-value images ($b=400\text{-}800s/mm^2$) of DWI. The model estimates a single diffusion coefficient value (dpADC) by summing the two ADCs weighted by a perfusion influence factor. The value of the factor may range from 0 to 1 and different dpADC estimates can be obtained by using different factor values. In the current study, analyses are performed using the factor values of 0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0.

A meta-analysis of thirteen studies evaluating the diagnostic performance of ADC in quantitative breast DWI from 964 lesions (615 malignant and 349 benign) demonstrates that pooled mean ADC from malignant lesions is significantly lower than that of benign lesions that may range from 0.87 to $1.61\times10^{-3}mm^2/s$ and the recommended ADC threshold for cancer diagnosis may vary from 0.90 to $1.76\times10^{-3}mm^2/s$ (27). In the current study, ADC estimations are performed by nonlinear fitting the mono-exponential model to average lesion signal intensity data to ensure high precision in the estimates (use of commonly preferred linear fitting complemented with log transformation in ADC estimations is reported to lower the precision (28)). The mean malignant lesion ADC and the optimal ADC threshold for cancer diagnosis are found to be $1.12\times10^{-3}mm^2/s$ and $1.61\times10^{-3}mm^2/s$, respectively, all in agreement with the literature. The optimal ADC threshold leads to misclassification of 29 lesions (24 benign and 5 malignant lesions) from 173 lesions (88 malignant and 85 benign) analyzed.

Mean dpADC from the malignant lesions is significantly lower than that of benign lesions independent of the perfusion influence factor used in the model that demonstrates a possible use of dual-phase ADC modelling in cancer diagnosis. The dual-phase ADC model with a perfusion influence factor of 0.5 offers the best performance among all the models. From this model, the mean malignant lesion dpADC is $1.07\times10^{-3}mm^2/s$ and the optimal dpADC threshold for cancer diagnosis is $1.50\times10^{-3}mm^2/s$. The model misclassifies 24 lesions (18 benign and 6 malignant lesions) from the 173 breast lesions analyzed.

One invasive ductal carcinoma, 1 liposarcoma, 1 ductal carcinoma in situ and 2 invasive mucinous carcinoma are misclassified by both ADC and dpADC. Use of dpADC lead to misclassification of one invasive lobular carcinoma additionally. On the other hand, 5 fibroadenomas, 4 abscesses, 3 adenoses, 2 columnar cell changes, 3 fibroses and 1 intraductal papilloma are misclassified by both ADC and dpADC. Use of ADC resulted in misclassification of other 6 benign lesions: 3 fibroadenomas, 1 abscess, 1 apocrine metaplasia and 1 columnar cell change. Dual-phase ADC modelling reduces the number of false-positive detections remarkably.

Some precautions should be considered for dpADC. Although dpADC of malignant lesions is significantly lower than that of benign lesions, mucinous carcinoma can reveal high dpADC values and can be misdiagnosed as benign while papilloma, abscess and fibrosis may demonstrate low dpADC values and therefore can be misdiagnosed as cancer. These shortcomings can be due to the underlying pathophysiology of these specific lesions. The mucinous carcinoma is among the malignant lesions, but it may reveal low cellularity and with relatively high-water content (29). Also, abscess, papilloma, and fibrosis are the benign lesions that may exhibit high cellularity (30). The current study imaging protocol schedules DWI before DCE-MRI scan and in the case of DWI immediately after DCE-MRI, presence of contrast agent in the tissue may lead to an artificial increase in dpADC from malignant lesions (A similar artificial increase has been recognized for ADC (30)).

During this retrospective study, a dedicated post-processing software has been developed and used to obtain the two separate ADC estimates within the dual-phase ADC model. However, the vendor-specif-

ic software packages installed on the main MR consoles are equipped with functionality to obtain different ADC maps (3) and can be set-up with little effort to obtain the maps required for dpADC modelling. This would facilitate the use of dpADC in clinic practice.

There are some limitations of the current study. The clinical utility of the dpADC for multi-centers and the repeatability and reproducibility of the dpADC from different brand MR scanners are questionable since this study enrolls breast lesions imaged using a 3.0T MR scanner at a single center. Small region-of-interests are placed for the breast lesions manually. This process requires utmost attention and experience especially for the lesions obscured with architectural distortion and if not performed precisely, may lead to a great variability in dpADC. The value of dpADC is calculated using two different ADC estimates and three different b-value images from DWI. More precise calculations can be accomplished with more number of images acquired with well selected b-values (20, 21). The current study has been designed to assess the best dpADC model in differentiating the breast masses using DWI only. Its use in clinical setting and value in multiparametric imaging complemented with dynamic contrast-enhanced MR imaging should be evaluated with further prospective studies.

In conclusion, dual-phase ADC modelling can provide almost the same sensitivity but considerably better specificity than traditional ADC calculations. Thus, dual-phase ADC modelling can improve the diagnostic accuracy of quantitative DWI in differentiating breast cancers from benign lesions. Requiring acquisition of only three different b-value images and benefiting from easy-to-setup ADC mapping tools installed on the main MR console, dpADC based evaluations can be easily adoptable to current imaging and evaluation protocols. Further prospective studies considering multiple institutions and multiple scanners are needed to justify its benefit in clinical setting and its value in diagnosis of breast lesions.

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

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

Peer-review: Externally peer-reviewed.

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

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Original Article

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Frequency of Rearrangements Versus Small Indels Mutations in *BRCA1* and *BRCA2* Genes in Turkish Patients with High Risk Breast and Ovarian Cancer

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ABSTRACT

Objective: The current rearrangement ratio of *BRCA1* and *BRCA2* genes is not known in the Turkish population. Rearrangements are not routinely investigated in many Turkish laboratories. This creates problems and contradictions between clinics. Therefore, the aim of this study was to evaluate the distribution and frequency of rearrangements in BRCA1 and BRCA2 genes in high-risk families and to clarify the limits of *BRCA1* and *BRCA2* testing in Turkey.

Materials and Methods: The study included 1809 patients at high risk of breast cancer or ovarian cancer. All patients were investigated for both small indels and rearrangements of BRCA genes using DNA sequencing and multiplex ligation-dependent probe amplification (MLPA) analysis.

Results: The overall frequency of rearrangements was 2% (25/1262). The frequency of rearrangements was 1.7% (18/1086) and 4% (9/206) in patients with breast cancer and ovarian cancer, respectively. The frequency of rearrangements was 3.7% (8/215) in patients with triple-negative breast cancer. The rearrangement rate was 7.7% (2/26) in patients with both breast and ovarian cancer.

Conclusions: Rearrangements were found with high rates and were strongly associated with bilateral and triple-negative status of patients with breast cancer, which are signs of high risk for breast and ovarian cancer. Analysis of rearrangements should definitely be included in routine clinical practice in Turkey for high-risk families and also for improved cancer risk prediction for families.

Keywords: High-risk breast and ovarian carcinoma, *BRCA1* and *BRCA2* genes, rearrangements, Turkish population

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Introduction

Breast cancer is the most common cancer among women worldwide and causes significant morbidity and mortality (1). According to the 2009 statistics of the Turkish Statistical Institute (TUIK), the leading cancer and the seventh-most-frequent cancer among women were breast and ovarian carcinoma, respectively. Among Turkish women, the incidence of breast cancer and ovarian carcinoma is 23% and 3.9%, respectively. Therefore, breast and ovarian carcinoma are important health problems for Turkish society. Furthermore, consanguineous marriages, especially among first cousins, are quite common in Turkey. This may lead to higher cancer risks, especially in families with cancer histories. It is very important to detect hereditary cancer risk using genetic testing for individuals in high-risk families as well as genetic testing, if applied correctly. Hence it is very important to determine the limits and content of genetic tests.

Several factors increase the risk of breast cancer such as family history, reproductive history, diet, hormone use, radiation exposure, obesity, sedentary lifestyle, lack of breast-feeding, and exogenous hormone replacement therapy (1). Among these, a family history with breast and ovarian cancer in several generations is present in about 15–20% of all cases (2). Germline mutations of two major tumor suppressor genes, *BRCA1* and *BRCA2*, are inherited in an autosomal dominant pattern and have links to breast and ovarian cancer (3). These two mutated genes increase the risk of breast cancer by 87% and 44% for ovarian cancer over the lifetime of female patients (4, 5). *BRCA1* and *BRCA2* participate in cellular functions such as cell growth, cell division, and genetic instability.

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Several syndromes are known to be involved in the development of breast and ovarian tumors such as hereditary breast and ovarian cancer syndrome, Li-Fraumeni syndrome, Cowden disease, hereditary non polyposis colon carcinoma (HNPCC), and Peutz-Jeghers syndrome (6). Nowadays, all cancer predisposing syndromes can be tested genetically, requested by either physicians or licensed genetic counselors. Clinical identification of these syndromes is beneficial in reducing the risk of cancer in mutation-carrying individuals. Affected persons can take preventative precautions such as screening, chemoprevention, or prophylactic surgery for the organ or tissue. Detected at early stages, prophylactic measures can be used for definitive cancer prevention (5). Genetic testing, genetic counseling, and the quality and ability of laboratories to test genes are significant factors.

In our study, we evaluated the rate of rearrangements of the genes *BRCA1* and *BRCA2* in 1809 patients at high risk for breast and ovarian carcinoma, as the current rearrangement rate is not known in the Turkish population. Rearrangements are not investigated in many Turkish laboratories in routine BRCA testing. We conducted the study to emphasize the importance of examining rearrangements while conducting *BRCA1* and *BRCA2* tests, and to determine the content and limits of the tests.

Material and Methods

General features of patient group: The Oncology Institute Breast and Ovarian Cancer patient cohort compromises high-risk patients having strong family history of cancer, early age of cancer diagnosis, triple negativity, bilateral breast cancer, multifocal localizations of tumor, mixed types of histology results, case of male breast cancer in family from every geographic region of Turkey between 1994 and 2016. 1809 cases were referred to our center from all geographic regions. The diagnoses of 1809 patients were confirmed with their histopathology reports before a genetic counseling session. Patients who agreed to *BRCA1* and *BRCA2* genetic testing were asked to complete a questionnaire regarding their family histories. High-risk patients were selected in accordance with the National Comprehensive Cancer Network (NCCN) criteria for breast/ovarian cancer. Informed consent was obtained from all participants in the study. The control group was included 125 healthy adults who have no family history on cancer and matched age, gender and ethnicity according to patients group. The study was approved by the Ethics Committee of Istanbul Medical Faculty at Istanbul University (2011/1425-681). The number of patients and patients' diagnoses in the study subgroups are given in Table 1. This work was supported by Istanbul University, Research Fund, Grant No: 21952 and GP-7/08122004 and Government Planning Organization of Turkey, Grant No: 97K121700.

Mutation analysis: Genomic DNA was isolated from 5 mL of peripheral blood lymphocytes using a QIAamp mini DNA extraction Kit (Qiagen, Inc.). All coding exons and adjacent intronic splice junction regions of *BRCA1* and *BRCA2* genes were screened for mutations in fragments between 197 to 823 bp length for Sanger Sequencing and about 450 bp length for Next Generation Sequencing (NGS) using a Multiplicome BRCA MASTR Dx Kit, which has a CE-IVD certificate in the MiSeq Illimuna Platform. A reference sequence of NM_007294.3 was used for the *BRCA1* gene, and NM_000059.3

Table 1. The frequency of rearrangements and overall mutations in all patients according to diagnosis in high risk breast and ovarian cancer cases in Turkey

Diagnosis of Patients	Number of Patients (n)	Rearrangements n(%)	Small Indel Mutations n(%)	Overall Mutation Rate n(%)
Overall Breast Cancer and Ovarian Cancer Cases	1809	25/1262(2%)	268/1785(15%)	293/1785(17%)
All Breast Cancer Cases	1473	18/1086(1.70%)	204/1473(13.8%)	222/1473(15.5%)
Unilateral Breast Cancer	1273	11/924(1.2%)	155/1273(12.2%)	166/1273(13.4%)
Unilateral Breast Cancer and Ovarian Cancer	33	2/26(7.7%)	16/33(48.5%)	18/33(56.2%)
Unilateral Breast Cancer and Other Type of Cancer	34	0/29(0.0%)	7/34(20.6%)	7/34(20.6%)
Bilateral Breast Cancer	90	5/85(5.9%)	20/90(22.2%)	25/90(28.1%)
Bilateral Breast Cancer and Other Type of Cancer	2	0/2(0%)	0/2(0%)	0/2(0%)
Male Breast Cancer	39	0/17(0%)	6/39(15.4%)	6/39(15.4%)
Male Breast Cancer and Other Type of Cancer	1	0/1(0%)	0/1(0%)	0/1(0%)
Bilateral Breast Cancer and Ovarian cancer	1	0/1(0%)	0/1(0%)	0/1(0%)
Triple Negative Breast Cancer	272	8/215(3.7%)	67/272(24.5%)	75/272(28.2%)
Patients having positivity in ER,PR,ErbB2(at least one)	971	5/741(0.7%)	108/971(11.1%)	113/971(11.8%)
All Ovarian Cancer Cases	370	9/206(4%)	81/370(22%)	90/370(24%)
Ovarian Cancer	326	7/170(4%)	65/326(19%)	72/326(23%)
Ovarian Cancer and Unilateral Breast Cancer	33	2/26(7.7%)	16/33(48.5%)	18/33(56.2%)
Ovarian Cancer and Endometrium Cancer	7	0/6(0%)	0/7(0%)	0/7(0%)
Ovarian Cancer and Other type of Cancer	3	0/3(0%)	0/3(0%)	0/3(0%)
Ovarian Cancer and Bilateral Breast cancer	1	0/1(0%)	0/1(0%)	0/1(0%)

was used for the *BRCA2* gene. All DNA sequencing results were read according to the hg19 genomic sequence. All patients and controls were tested for the presence of small indel mutations and rearrangements. 1809 probands, diagnosed breast and ovarian cancer, and 125 healthy controls were sequenced for the full exons of *BRCA1*and *BRCA2* genes with Sanger Sequencing using Dye terminator Cycle sequencing (DTCS) kit (Beckman Coulter, CEQ8000 and GXL, USA) and BigDye Terminator (Applied Bioscience Inc., USA) systems. A total of 741 probands were analyzed using a Multiplicom BRCA MASTR Dx kit on an Illimuna MiSeq platform. All bioinformatic analyses were executed using Sophia Genetics. The analysis took into account the variants with a coverage ratio ≥ 300X and "Allele Variant/ Coverage" ≥0.2.

The data from NGS analysis was evaluated by using different types of bioinformatics software which were Variant Studio, Sophia Genetics and Genomize to classify the mutations in 5 different categories. The categorized alterations were checked in different databases which were HGMD (Human Genome Mutation Database), dbSNP (The singe nucleotide polymorphism database), ClinVar (Public archive of interpretations of clinically relevant variants) and Alamut (Interactive biosoftware) for clinical importance after classification.

Multiplex ligation-dependent probe amplification (mlpa) and copy number variation (cnv) analysis: We evaluated rearrangements using both the MiSeq NGS platform and MLPA analysis. To calculate CNVs, 300X coverage was used. MLPA analysis was also used to confirm the CNV results from the MiSeq Illumina. MLPA analysis was performed using MRC-Holland probe sets for *BRCA1* (P087/P002) and *BRCA2* (P045/ P077) genes. The manufacturer's instructions were followed. At least one negative and three normal controls were run in each experimental batch, including DNA molecular weight markers. Amplified DNA was run on a Beckman Coulter DNA sequencer (Beckman Coulter, CEQ8000 and GXL, USA) for fragment analysis. Row data of fragment analyses were analyzed using Coffalyser analysis software and peak areas were calculated using a Coffalyser algorithm. All experiments per patient were performed using four probe sets for both *BRCA1* and *BRCA2* genes to avoid false-negative and positive results, and to confirm deletions and duplications.

Positive results for pathogenic mutations were repeated with two independent experiments using two probe sets for each gene. Confirmation analysis of rearrangement results from NGS data was replicated by using MLPA analysis with two probe sets for each gene. Confirmation analysis of rearrangement results from MLPA analysis was repeated using MLPA analysis in two independent experiments using both normal and confirmation probe sets for each gene. All positive results were confirmed at least five times in our data set.

All genetic tests were run in the laboratory of Cancer Genetics Department in Oncology Institute. The laboratory is a reference center for BRCA testing in Turkey for both genotyping and genetic counseling.

Statistical analysis

Statistical analysis was performed with Statistical Packages for the Sıcial Sciences (SPSS) version 20 (IBM Corp.; Armonk, NY, USA)**.** Demographic and clinical features of 1809 patients in our cohort were compared with BRCA mutation status using Chi-square tests. The rearrangements prevalence was calculated for the cohort defined by age and family history.

Results

We searched for patients at high-risk of breast and ovarian cancer across seven different regions of Turkey in order to evaluate the prevalence and spectrum of rearrangements of *BRCA1* and *BRCA2* genes. We also aimed to emphasize the importance of examining rearrangements while conducting *BRCA1* and *BRCA2* tests, and to determine the content and limits of the tests.

Families were selected according to the NCCN criteria for breast/ovarian cancer. In the cohort, the patients with breast and ovarian cancer have family histories with breast, ovarian and other types of cancer at first and second-degree relatives mostly. All patients were investigated for both small indels and rearrangements of BRCA genes using DNA sequencing and MLPA analysis. Both CNVs and MLPA assays were used to detect the rearrangements of *BRCA1* and *BRCA2* genes. The study included 1809 patients, who were identified and confirmed through the cancer genetics clinic in our institution by a genetic counselor and a physician according to NCCN criteria.

The number of patients and the distribution of patients according to their diagnoses are given in Table 1. The mean age at diagnosis was 41.9±9.9 years for BRCA non-carriers and 40.6±9.7 years for carriers with *BRCA1* rearrangements in the cohort. Rearrangements in *BRCA1* were observed in 25 of 1809 (1.4%) patients with breast and ovarian cancer who had a high-risk family history. All rearrangements in our study population were found in the *BRCA1* gene. No *BRCA2* rearrangements were found among the 1809 patients. However, four BRCA mutations (3.2%) were found in the healthy controls.

The overall frequency of mutations (small indels and rearrangements) in *BRCA1* and *BRCA2* genes of patients at high-risk for breast and ovarian cancer was 17% in the cohort. In patients with a high risk of breast cancer, the total frequency of all mutations and rearrangements in *BRCA1/2* genes was 15.5% (222/1473) and 1.70% (18/1086), respectively. The highest frequency of rearrangements among patients with breast cancer was 7.7% (2/26) in patients who had ovarian carcinoma as a secondary tumor. The frequency of rearrangements was also high in patients with triple-negative breast cancer (3.7%, 8/215). Rearrangements were found in 5.9% (5/85) of patients with bilateral breast cancer. No rearrangements were detected in Turkish patients with male breast cancer although the overall *BRCA1* and *BRCA2* gene mutation rate was 15.4% (6/39) in that subgroup (Table 1). A total of 293 mutations were identified in the 1809 patients with breast/ovarian cancer (Table 2). Of these, 189 patients had frameshift mutations with a frequency of 63.5%. The frequency of nonsense mutations was 16%. The percentages of missense and splice error mutations were 5.8% and 6.2%, respectively (Table 2).

The overall mutation frequency of patients with ovarian cancer was 24% (90/370) for both small indels and rearrangements. The frequency of rearrangements in Turkish patients with ovarian cancer was found as 4% (9/206). The rearrangements percentage was 4% (7/170) in patients who had ovarian tumors only. The subgroups of patients with ovarian cancer and other types secondary tumors revealed no rearrangements.

A total of 25 rearrangements in *BRCA1* were identified among the 1809 patients. We found that 2% (25/1262) of Turkish patients with a family history of breast and ovarian cancer had rearrangements in the *BRCA1* gene. Sixteen rearrangements were observed in patients with breast cancer with a frequency of 64% (16/25). Nine of the detected

BRCA1 gene rearrangements were in ovarian cancer (36%, 9/25) and eight were in triple-negative breast cancer (62%, 8/13) (Table 3).

Table 2. The types of overall mutations and their percentages found in our study group

Types of mutations	BRCA1/BRCA2 mutation positive cases n(%)
Frameshift	186 (63.5%)
Nonsense	47 (16%)
Missense	17 (5.8%)
Rearrangement	25 (8.5%)
Splice error	18 (6.2%)
Total mutation	293

Table 3. Distribution of rearrangements according to diagnosis

Distributions of rearrangements according to diagnosis	
Diagnosis	**Number of rearrangements (%)**
Breast Cancer Cases	(16/25)(64%)
Ovarian Cancer Cases	(9/25)(36%)
Triple Negative Breast Cancer Cases	(8/13)(62%)
Total	25

Table 4. Types of rearrangements and their percentages found in our study group

Distribution of the different types of rearrangements in the Cohort	
Types of rearrangements	**Numbers of rearrangements (%)**
All Deletions	21(84%)
All Duplications	4(16%)
Exon 1-2 Deletion	1 (4%)
Exon 1-3 Deletion	1 (4%)
Exon 1-21 Deletion	3 (12%)
Exon 10-24 Deletion	1 (4%)
Exon 18-19 Deletion	10 (40%)
Exon 21-22 Deletion	1 (4%)
Exon 24 Deletion	2 (8%)
Exon 1-15 Deletion	1 (4%)
Exon 14 Deletion	1 (4%)
Exon 3-8 Duplication	1 (4%)
Exon 5-9 Duplication	1 (4%)
Exon 10-12 Duplication	2 (8%)
Total	25

Twenty-five *BRCA1* gene rearrangements were detected in our cohort (details are given in Table 4). Overall, 84% (21/25) of deletions and 16% (4/25) of duplications were detected among the rearrangements (Table 4). The most common alteration (10/25) was exon 18-19 deletion (Table 4) (Figure 1). The frequency of exon 18-19 deletion was 40% (10/25) in patients with a family history of breast and ovarian cancer, and all patients with mutations lived in the Black Sea region of Turkey. The second most common rearrangement was exon 1-21 deletion, which was seen with a frequency of 12% (3/25) in our cohort. The remaining thirteen different mutations were detected with frequencies of 4–8%.

The average age at diagnosis, histopathology, and family histories of patients among carriers of *BRCA1* gene rearrangements are given in Table 5. The mean age at diagnosis was 40.6±9.7 years for *BRCA1* rearrangement carriers. Of 18 patients, 16 patients with breast cancer had invasive ductal carcinoma (IDC), one had invasive lobular carcinoma (ILC) and one had ductal in situ carcinoma (DCIS). With the exception of one patient, all patients with ovarian cancer had serous histopathology.

Deletions of both exons 1-21 and 18-19 were found frequently in our study group. All patients who carried *BRCA1* gene exon 1-21 deletions had a strong history of breast cancer. In addition to four cases of breast cancer in all of these families, there was at least one case of ovarian cancer, and also other types of cancer in all patients with mutated exon 1-21 deletions who lived in the Marmara region. When we examined the family history of patients with exon 18-19 deletions, there was at

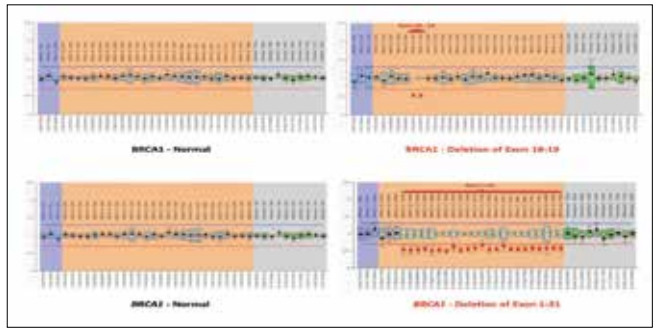

Figure 1. Results of MLPA analysis for *BRCA1* gene. (Left Upper): Patient DNA have a normal copy number of *BRCA1* gene; (Right Upper): Patient DNA with the deletion of exon 1-21 region of *BRCA1*gene; (Left Lower): Patient DNA with a normal copy number of BRCA1 gene; (Rigth Lower): Patient DNA with the deletion of exon 18-19 region of *BRCA1* gene

Figure 2. Distribution of *BRCA1* LGR mutations according to geographic regions of Turkey

Table 5. The family histories, age at diagnosis, clinical and histopathologic features of carriers with the rearrangements

The rearrangements of BRCA1 gene in Turkish High-Risk Breast and Ovarian Cancer Cases					
Patients	**Rearrangements**	**Diagnosis**	**Histopathology**	**Age at Diagnosis**	**Family History**
BR1487	Deletion of Exon 1-21	Breast Carcinoma	ILC	33	4BC+2OC+4OTC
BR1500	Deletion of Exon 1-21	Breast Cancer and Ovarian Cancer	IDC + Serous	42	4BC+1OC+1OTC
BR1589	Deletion of Exon 1-21	Breast Carcinoma	IDC	51	4BC+1OC+4OTC
BR1428	Deletion of Exon 18-19	Breast Carcinoma	IDC	50	1BC+4OC+5OTC
BR1679	Deletion of Exon 18-19	Breast Carcinoma	IDC	51	5BC+3OTC
BR1745	Deletion of Exon 18-19	Breast Carcinoma	IDC	30	2BC+1OTC
BR1903	Deletion of Exon 18-19	Breast Carcinoma	IDC	42	2BC+1OC+8OTC
BR1753	Deletion of Exon 18-19	Breast Carcinoma	DCIS	31	2BC+2OC+5OTC
BR1462	Deletion of Exon 18-19	Breast Cancer and Ovarian Cancer	IDC + Serous	41	3BC+1OC+2OTC
BR1508	Deletion of Exon 18-19	Ovarian Carcinoma	Serous	34	4OC+7OTC
BR1509	Deletion of Exon 18-19	Ovarian Carcinoma	Serous	49	3OC+5OTC
BR1592	Deletion of Exon 18-19	Ovarian Carcinoma	Serous	51	1BC+5OC+5OTC
BR1609	Deletion of Exon 18-19	Ovarian Carcinoma	Adenocarcinoma	36	2OC+ 1OTC
BR2064	Deletion of Exon 1-2	Bilateral Breast Carcinoma	IDC	46	1BC+1OC+2OTC
BR0527	Deletion of Exon 1-3	Bilateral Breast Carcinoma	IDC	35	1BC+3OTC
BR1488	Deletion of Exon 10-24	Ovarian Carcinoma	Serous	55	1BC+1OC+8OTC
BR1291	Deletion of Exon 21-22	Breast Carcinoma	IDC	25	4OTC
BR2231	Deletion of Exon 1-15	Breast Carcinoma	IDC	34	1BC+3OTC
BR1667	Deletion of Exon 24	Bilateral Breast Carcinoma	IDC	33	1OC+3OTC
BR1839	Deletion of Exon 24	Ovarian Carcinoma	Serous	64	3BC+2OC
BR2474	Deletion of Exon 14	Bilateral Breast Carcinoma	IDC	38	1OC+1OTC
BR2451	Duplication of Exon 10-12	Bilateral Breast Carcinoma	IDC	42	1BC+1OTC
BR1814	Duplication of Exon 10-12	Breast Carcinoma	IDC	31	2OTC
BR2037	Duplication of Exon 3-8	Breast Carcinoma	IDC	27	1BC+1OC+3OTC
BR1556	Duplication of Exon 5-9	Ovarian Carcinoma	Serous	45	4OC+1OTC

IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; DCIS: ductal carcinoma in situ; BC: breast carcinoma; OC: ovarian carcinoma; OTC: other types of cancer

least one case of other cancers in the majority of families. In addition, cases of breast cancer and many ovarian cancers were observed. It was determined that all patients who carried exon 18-19 deletions were born and lived in the Black Sea region (Figure 2). There were only four large duplications found in patients with breast cancer and ovarian cancer.

The distribution of patients with carriers of rearrangement according to geographic regions of Turkey were 59.1% in the Black Sea region, 27.3% in the Marmara region, 4.5% in the Eastern Anatolia region, and 9.1% in the Central Anatolia region (Figure 2). Even though there were small indel mutations in the remaining three regions, no rearrangements were found.

Discussion and Conclusions

Three previous studies have detected rearrangements in the Turkish population. The first study was based on with 667 unselected patients with ovarian cancer and 27 rearrangements were found with a frequency of 4%. Most (25/27) rearrangements were found in patients with hereditary ovarian cancer (7). The rearrangement ratio (40.9%) given by Aktaş et al. (7) for patients with ovarian cancer who had family histories was very high according to the international literature (4, 7-17). The second study investigated the rearrangement ratio in patients with hereditary breast cancer, but with a small sample size. In the study, only 16 patients with hereditary breast cancer were investigated for rearrangements and none was observed. Manguoğlu et al. (18) suggested that the rearrangement percentage could have been low because of the small sample. The last study was performed by Aydın et al. (19) who tested 211 unselected patients with breast cancer who lived in the Black Sea region. Their rearrangement frequency was 1.9% and their findings gave no information about the rest of the country and hereditary ovarian cancer. All authors suggested that comprehensive studies should be performed in the Turkish population.

Hence there are no clear results about rearrangement ratios in the Turkish population. Consequently, the rearrangement of *BRCA1* and *BRCA2* genes are not routinely investigated in most clinical genetics laboratories in Turkey. This leads to conflicts between clinics and institutional laboratories, and it also affects the correct management of patients. *BRCA1* and *BRCA2* mutation screening is becoming more important in clinical practice for treatment options such as PARP inhibitors. The effective management of patients at high risk for breast and ovarian cancer depends on the identification of all mutations such as small indels and rearrangements, which can be screened using different molecular techniques or deep coverage. The knowledge of mutations could be used for risk reduction and chemoprevention as well as treatment options in patients and their relatives. Therefore, this study's goal was to identify the percentage of rearrangements in Turkish patients at high risk for breast and ovarian cancer within a large cohort and to ensure compatibility between laboratories in Turkey.

Many studies have revealed rearrangement frequencies with wide variations for different populations around the world. Judkins et al. (4) found that the rearrangement percentage was 6–10% for all mutations in *BRCA1* and *BRCA2* genes. Palma et al. (11)reported rearrangements a frequency of 18% in a specific population. Arnold et al. (20) found that rearrangements accounted for 12.7% in an admixture American population. Kwong et al. (17) showed that the rearrangement rate was 8.7% in the Chinese population. French and Czech population frequencies were 6–7.7%, and a high frequency of *BRCA2* gene rearrangements was determined in the French population (15). Rearrangement frequencies were between 3–3.7% in Australian and Korean populations (9, 13). Gutierrez-Enriquez et al. (10) detected 1.5% rearrangements in the Spanish population. The rearrangement rate was 0–1% in Chilean, Sri Lankan, and Finnish populations (12, 14, 16). However, there are still no clear data for many specific populations and laboratories that perform BRCA testing using only DNA sequencing or both DNA sequencing and rearrangement testing, which poses problems in terms of the selective use of treatments such as risk reduction surgery, preventive medicine, chemoprevention, and specific drugs such as PARP inhibitors.

In our study, the rearrangement of *BRCA1* and *BRCA2* genes were investigated using CNV analysis with next-generation sequencing and MLPA analysis in 1809 Turkish patients at high risk for breast and ovarian cancer. Among the 1809 patients, we detected only 25 *BRCA1* gene rearrangements with a frequency of 2% (25/1262) versus 15% (268/1785) small indel mutations. Our findings indicate that it would be beneficial to test patients with high-risk family histories to better estimate the probability of mutations.

We found that all rearrangements were located on the *BRCA1* gene in our cohort. Our results confirmed the higher prevalence of rearrangements in the *BRCA1* gene versus the *BRCA2* gene documented in previous reports (21-25).

In our study group, the rearrangement rate was high in patients with ovarian cancer (4%, 9/206), triple-negative breast cancer (3.7%, 8/215), bilateral breast cancer (5.9%, 5/85), and patients with breast and ovarian cancer (7.7%, 2/26). Therefore, in high-risk patients, rearrangement testing should be included in standard *BRCA1* and *BRCA2* gene tests. Furthermore, it was determined that the frequency of rearrangements differed across various geographic regions in Turkey.

In our study, exon 18-19 deletion was the most common rearrangement and all mutation carriers were born and lived in the Black Sea region. Aktaş et al. (7) and Aydın et al. (19) reported the same mutation with a low percentage in a small group of patients from the same region Therefore, we think that exon 18-19 deletion could be a regional alteration specific to the Black Sea region. However, exon 18-19 deletions (40%, 10/25) were the most frequent rearrangements in our cohort. Exon 1-2 deletions (27.8%) were the most common rearrangements in the study by Aktaş et al. (7) in a Turkish population. However, their study group was very small, with 61 patients at high risk for ovarian cancer. In our study, half of the exon 18-19 deletion carriers were diagnosed as having breast cancer, the other half had ovarian cancer. When we examined the family history of patients with exon 18-19 deletions, there was at least one case of other cancers in the majority of families. In addition, there were breast and ovarian cancers.

The second most common mutation was the exon 1-21 deletion (12%, 3/25), which was found in patients living in the Marmara region. All exon 1-21 deletion carriers had breast cancer, and at least 4 cases of breast cancer and one case of ovarian cancer, and other types of cancer were seen in their families.

The cohort included 39 male patients with breast cancer. No rearrangements were found in this subgroup, although the percentage of small indel mutations was 15.4% (6/39). The studies performed by Manguoğlu et al. (18) and Falchetti et al. (26) also showed that there were no rearrangements in breast cancer in Turkish and Italian men, respectively. Another study in a Brazilian population showed that the rearrangement rates in men with breast cancer were less than 1% (27).

In conclusion, rearrangements found in the *BRCA1* gene were present in a considerable proportion of the mutations detected among women who were being treated at a cancer genetics clinic for breast and ovarian cancer risk assessment. Some rearrangements are more common in specific regions of Turkey. Patients at high risk for ovarian cancer, triple-negative breast cancer, and bilateral breast cancer, and patients with breast and ovarian cancer should be tested for rearrangements. Furthermore, the analysis of rearrangements should be part of *BRCA1* and *BRCA2* testing and a standard application for Turkish patients at high risk for breast and ovarian cancer.

According to our results, there is no longer any doubt as to whether rearrangements should be tested in patients at high risk for breast and ovarian cancer in Turkey. Rearrangement testing should include *BRCA1* and *BRCA2* analyses in all routine genetic tests in Turkey. We think that our results have clarified the limits and contents of *BRCA1* and *BRCA2* testing in Turkey.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Istanbul University, İstanbul School of Medicine (2011/1425-681).

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

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Original Article

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Biological Subtypes of Breast Cancer and Sentinel Lymph Node Biopsy

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ABSTRACT

Objective: Breast cancer subtypes are used as prognostic and predictive factors considering the genomic profile of the disease. This study is designed to investigate the Sentinel Lymph Node (SLN) detection rate in breast cancer for different biological characteristics.

Material and Methods: Patients on whom we performed the methylene blue method alone were named as Group I, radiocolloid substance method alone as Group II and both methylene blue and radiocolloid method as Group III. The results of biological tumor characteristics and characteristics of the patients on different SLN biopsy techniques were investigated.

Results: The overall SLN detecting success rate was 83.3%. When considered for each group, success rate was 80% for group I, 84.9% for group II and 90.6% for group III. While a success rate of 94.6% was achieved with radiocolloid only in the patients in Luminal A and B subgroup, 90% success rate was achieved in Her2 (+) and triple negative (TN) patients with combined method.

Conclusion: While successful results could be achieved by using radiocolloid substances alone in patients with Luminal A and B subtypes, combined methods should be used in HER2 (+) and TN patients.

Keywords: Breast cancer, methylene blue, radiocolloid, sentinel lymph node biopsy

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Introduction

Axillary lymph node dissection is still part of breast cancer surgery to determine the prognosis and appropriate treatment; however, it is also the most important reason for surgical morbidity. Sentinel lymph node (SLN) concept in practice currently means avoiding axillary node dissection and associated morbidity.

Sentinel lymph node that are negative for tumor cells reflect that the remaining axilla is also tumor-free, there by allowing the surgeon to avoid unnecessary dissection and reduce morbidity. Different techniques are being used to detect axillary SLN's intraoperatively, including vital dyes like isosulfan blue, methylene blue, and patent blue dye, as well as various pharmaceuticals that make lymph nodes visible and easily detectable. Each of these methods have a different success rate for detecting SLN's, and combinations of some methods can increase this rate.

Breast cancer is a heterogeneous disease with distinct clinical and biological features. Subtypes based on the genomic profile of the disease are used as prognostic and predictive factors. The Ki-67 proliferative index and features of the molecular biological subtypes are the most appropriate criteria for the choice of treatment today. Biological differences between tumor groups may affect the technical characteristics related to sentinel lymph node biopsy (SLNB).

The present study was designed to investigate the SLN detection rate in breast cancer based on different biological characteristics of tumors to determine the best SLNB technique for different breast cancer subtypes.

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Materials and Methods

In this prospective study, we evaluated 287 invasive breast cancer patients (250 invasive ductal carcinoma, 21 invasive lobular carcinoma, 9 mucinous carcinoma and 7 invasive tubular carcinoma) between February, 2006 and March, 2010. We performed breast-conserving surgery and SLN dissection to predict axillary involvement. Written consent was obtained from all suitable patients for breast-conserving surgery and SLN dissection.

We classified our patients into subtypes following the Saint Gallen criteria: Luminal A [ER (+) and/or PR (+), HER2- and Ki-67<14], Luminal B [ER (+) and/or PR (+), HER2 (+) and/or Ki-67≥14], Erb-B2 [ER-, PR- and HER2 (+)] and Triple Negative (TN) [ER-, PR- and HER2-] (1).

Table 1. Patient Characteristics in Chi-Square Test According to Biological Subtypes

	Luminal A (100) n (%)	Luminal B (121) n (%)	TN + Her2 (+) (66) n (%)	p
Age				
Age<40	15 (15%)	19 (16%)	14 (21%)	
40≤Age<50	39 (39%)	46 (38%)	24 (36%)	0.08
Age≥50	46 (46%)	56 (46%)	28 (42%)	
Biopsy Method				
Excisional	77 (77%)	83 (69%)	53 (80%)	
Incisional	10 (10%)	18 (15%)	4 (6%)	0.09
Tru-cut and FNA	13 (13%)	20 (16%)	9 (14%)	
Tumor Location				
Upper Outer Quadrant	74 (74%)	87 (72%)	49 (74%)	
Upper Inner Quadrant	12 (12%)	14 (11%)	8 (12%)	0.4
Lower Outer Quadrant	7 (7%)	11 (9%)	5 (7%)	
Lower Inner Quadrant	7 (7%)	9 (8%)	4 (7%)	
Tumor Size				
T1	25 (25%)	31(26%)	17 (26%)	
T2	58 (58%)	69 (57%)	38 (58%)	0.7
T3	17 (17%)	21 (17%)	11 (16%)	
Ki-67				
0-14	21 (21%)	25 (20%)	12 (18%)	
15-30	49 (49%)	50 (41%)	31 (47%)	0.5
>30	24 (24%)	37 (31%)	19 (29%)	
Unknown	6 (6%)	9 (7%)	4 (6%)	
SLNB Technique				
Methylene Blue	64 (64%)	76 (63%)	30 (46%)	
Radiocolloid Substance	17 (17%)	20 (17%)	16 (25%)	0.4
Combined Method	19 (19%)	25 (20%)	20 (29%)	

FNA: fine needle aspiration; SLNB: sentinel lymph node biopsy; TN: Triple negative

We performed three different methods to detect SLN's intraoperatively—methylene blue, radiocolloid substance, and a combined method—and evaluated the success rates of each patient. One of the three SLN detection techniques were applied to the each patient respectively, as methylene blue technique to the first patient, radioisotope colloid to the second patient and combined technique to the third patient, and proceeding to the next patients sequentially.

For the patients whose SLN detection technique would be achieved by methylene blue only or combined technique, 4-6cc of 1% methylene blue solution was applied subdermally to the periareolar and peritumoral region before the surgical procedure started. Following the injection, we waited for 10 minutes and then searched for blue-stained lymph nodes in the axillary region. For the patients whose SLN detection technique would be achieved by radioisotope colloid only or combined technique; 1 mCi Tc-99m nanocolloid was applied peritumorally and/or intradermally 4-12 hours before surgery, and preoperative lymphoscintigraphy was performed on these patients to determine involvement of the lymph nodes.

Lymphnodes detected by gamma detectors or stained blue (either the node itself or the surrounding lymph channels) were considered SLN's. After removal of the SLN, the surgical field was screened again with the gamma detectors and activity less than 10% of the highest (hottest) lymphnode activity was considered back ground activity.

Ethics committee approval was received for this study from the ethics committee of Ankara Oncology Hospital (Decision Date: 12.01.2006, Decision Number: AOH-211/2006).

Statistical calculations were performed using Statistical Packages for the Social Sciences (SPSS) for Windows version 16.0 (SPSS Inc., Chicago, IL, USA). Chi-square test is used for comparing patient characteristics (age, menopause status, biopsy and SLNB technique) and tumor characteristics (size, localization, Ki-67 status) with biological tumor subtypes. Logistic regression analysis is used to determine the efficacy of SLNB technique according to biological tumor subtypes and other parameters. The level of significance was set at $p<0.05$.

Results

The study included 287 patients with breast cancer. All the participants were women. The mean patient age was 50.2 years. According to the biological subtypes, 100 patients (35%) were luminal A type, 121 patients (42%) were luminal B type, 43 patients (15%) were TN type, and 23 patients (8%) were Her2 (+) type. Biological subtypes sorted by the patient and tumor characteristics are given in Table 1.

The overall success rate for SLN detection was 83.3% for all patients. We detected at least 1 SLN in 239 of 287 patients and could not find any node in 48 (16.7%) patients. The success rate was 80% for patients whose SLN detection technique was methylene blue only, 84.9% for patients whose SLN detection technique was radioisotope colloid only, and 90.6% for patients whose SLN detection technique was the combined method.

According to patient age, the success rate was 79% (n=34) in patients aged 40 years, 83.4% (n=91) for patients aged 40–50, and 84% (n=114) for patients over the age of 50. The success rate was 84% (n=117) for the premenopausal group and 82.4% (n=122) for the postmenopausal group.

The overall success rate was 83.7% (n=180) for patients who had excisional biopsy primarily, and 78.1%, 83.3%, and 87.5% for incisional, tru-cut, and fine needle aspiration (FNA) biopsies, respectively.

Table 2. Factors Affecting Success Rates in Univariate Analysis

Factor		Success rate (%)	p
Tumor localization	UOQ	84.7	0.09
	UIQ	70.5	
	LOQ	82.6	
	LIQ	90	
Primary biopsy method	Excisional	83.7	0.085
	Incisional	78.1	
	Tru-cut	83.5	
	FNA	87.5	
Patient age	<40	79	0.121
	40-50	83.4	
	>50	84	
Tumor size	T1	80.8	0.41
	T2	86	
	T3	85.7	
Ki-67 proliferative index	0-14	80.3	0.32
	15-30	82.1	
	>30	86.8	
Menopausal status	Premenopausal	84	0.22
	Postmenopausal	82.4	
Biological subtypes	Luminal A-B	86.5	0.02
	TN- Her2(+)	72.8	
SLN detection method	Methylene Blue only	80	0.04
	Radiocolloid only	84.9	
	Combined	90.6	

UOQ: Upper Outer Quadrant; UIQ: Upper Inner Quadrant; LIQ: Lower Inner Quadrant;
LOQ: Lower Outer Quadrant; TN: Triple negative; FNA: Fine Needle Aspiration; SLN: sentinel lymph node

Table 3. Factors Affecting Success Rates in Multivariate Analysis

Factor	p	95% Confidence interval		Odds Ratio
		Lower	Upper	
Biological subtypes	0.014	1.042	5.419	3.57
SLN detection method	0.032	1.351	9.714	2.18

SLN: Sentinel Lymph Node

The overall success rates were 84.7, 70.5, 82.6, and 90% for the upper outer quadrant (UOQ), upper inner quadrant (UIQ), lower outer quadrant (LOQ), and lower inner quadrant (LIQ) tumors, respectively. The overall success rates were 80.8, 86, and 85.7% for T1, T2, and T3 tumors. The Ki-67 proliferative index showed overall success rates of 80.3, 82.1, and 86.8% for tumors with indexes of 0-14, 15-30, and greater than 30, respectively.

Univariate analyses showed that age, menopause status, tumor size, Ki-67 index and tumor localization have no effects on SLNB detection rate. Factors influencing SLNB detection rate is found to be biological tumor subtype and SLN detection method in both univariate and multivariate analysis (Table 2, 3). Because of their biological features and number of patients, luminal A and B tumors and TN and Her2 positive tumors are stratified as two separate groups.

Sentinel Lymph Node could not be detected in 10 of 30 patients (33%) in the Her2 (+) and TN group and could not be detected in 24 of 140 patients (17%) in the Luminal A and B groups when the SLNB was only performed with methylene blue. In patients where the SLNB was performed only with radiocolloid, a SLN could not be detected in 2 of 37 patients in the Luminal A and B groups (5.4%). This rate was 37.5% for patients in the Her2 (+) and TN groups. When the combined method was used, a SLN could not be detected in 9% of the Luminal A and B patients and in 10% of the Her2 (+) and TN groups. When only blue dye or radionuclide was used, SLN detection rate was found to be significantly lower in TN and Her2 (+) groups compared to luminal A and B groups. This difference disappeared when combined methods were used to detect SLN in TN and Her2 (+) patients.

Discussion and Conclusion

Different techniques have emerged to achieve SLN detection. The literature indicates that application of radiocolloid substances and use of gamma probes and lymphoscintigraphy raise the success rates. The present study found a success rate for radiocolloidalone of 84.9% in agreement with the findings of Krag et al. (2) who reported an 82% success rate using a Tc 99m sulfide colloid and a gamma probe in a study of 18 patients. This technique seems easier and less time-consuming than methods using vital dyes. In 1997, Pijpers et al. (3) showed a 97.8% success rate with Tc 99m colloid albumin and concluded that methods with radioactive colloidal substances were better and easier than methods with vital dyes for determining SLN's. In the same year, Veronesi et al. (4) achieved a 98% success rate with radiocolloid alone. Gulec et al. (5) showed a 94%success rate with Tc 99m sulfide colloid alone and concluded that radiocolloid method is less time consuming than vital dye methods. Dunnwald's study with 93 patients reported a rate of 85% (6). The differences in rates between reports are due to the radioactive substance used, its activity, its injection volume, and location of injection.

Pijpers et al. (7) suggested that success rates in malignant melanoma patients could be increased by combining vital dye and radiocolloid methods .Cox et al. (8) confirmed this result for breast cancer in their guideline study, where they found SLN's in 440 of 466 patients (94.4%) with a combined method, and they concluded that a combined method was superior. Liberman et al. (9) suggested that a combined method was superior to the individual methods alone upon achieving a success rate of 91%. Similar to our study findings, in 1999, Hill divided 500 patients into three groups and showed success rates of 80, 85, and 93% for blue dye, isotope, and combined groups, respectively (10).

In our study, we also evaluated the factors that could affect the SLN detection rate, including age, menopausal status, tumor location, size, primary biopsy method, Ki-67 proliferative index, breast cancer subtypes and SLN detection technique. The EORTC 10981-22023 AMAROS study identified 1953 patients who were suitable for SLNB and reported a success rate of 97%. They indicated once again that a combined method was better than the individual methods used alone. They suggested that factors affecting these rates included age, pathologic tumor size, tumor histology, year of the procedure, and preferred method (11). Some reports suggest that SLN detection rates decrease with patient age. McMasters et al. (12) indicated that success rates significantly decreased at ages over 50, while Chakera et al. (13) found similar results at age over 56 and Chagpar et al. (14) reported decreases at age over 60 in a study of 4151 patients. The age-dependent success rates reflect the increase in axillary fat tissue and decrease in of lymphatic flow with age (15), as the increase in fat tissue in lymph nodes with age can decrease the passage of vital dyes or radiocolloid substances (16). Similarly, the AMAROS study reported a decrease in the success rate in patients over age 70, but the highest achieved rates were in patients aged between 50 and 69 years. In our study, the success rate was higher in patients over 50 years old than in younger ones. This difference in age ranges can be attributed to fewer numbers of younger patients in the studies. Koizumi et al. (17) concluded that factors that affect the involvement of radioactive substance in SLN's include the body mass index, age, and menopausal status. In our study, we found no difference among the groups according to menopausal status.

The literature contains some reports suggesting that the primary biopsy method, could affect SLN detection (16). However, Miner et al. (18) found that the primary biopsy method had no effects on SLN, and Marchal et al. (19) came to the same conclusion in 2006. However, patients with a previous excisional biopsy might be expected to show a lower success rate due to disrupted lymphatic flow around the tumoral tissue. Although SLN detection rates were the lowest in patients who underwent incisional biopsy in our study, no significant difference was encountered among different biopsy techniques.

Detection of SLN is relatively more difficult in inner quadrant tumors because of masking of internal mammary nodes by the injection site. The long distance between inner quadrant tumors and axillary lymph nodes also imposes a longer waiting time for the delivery of vital dyes or isotopes to the nodes. Krag et al. (16) showed that the success rates are lower in inner quadrant tumors, independent of the SLN detection technique. Morrow et al. (20) suggested that the highest success rate for SLN's is obtained for upper outer quadrant tumors. In our study group, the best success rate was in the lower inner quadrant, but this could be due to the lower number of patients in that group.

Marchal et al. (19) showed that tumor size has no effects on detection of a SLN. Morrow et al. (20) suggested the same result in their studies. However, all these researchers agreed that the success rates decrease in non-palpable tumors. In our study, the overall success rates did not change according to tumor size.

High tumor grades are correlated with an increase in the number of metastatic nodes. In the presence of metastatic lymph nodes, the lymphatic blockade by tumor cells prevents the flow of dye or radiocolloid. For this reason, the SLN success rate would theoretically be expected to decrease with increases in tumor grade. Hence, Marchal et al. (19) suggested that success rates were lower in patients with lower grade. Currently, the Ki-67 tumor proliferative index is also widely used for tumor grading. In our study, we found no correlation between the success of SLN detection and this parameter.

A number of histological, molecular, and biological characteristics, as well as traditional prognostic factors, are longer decisive in the locoregional treatment of breast cancer (21, 22). We know that TN or Her2 (+) patients carry a higher risk of SLN metastasis than do the patients in the luminal group. This risk can be up to six times greater, especially in TN patients (21). The low SLN detection rates in this group of patients with methylene blue or radiocolloid substances alone could be associated with this high metastasis rate. Lymphatic tumor emboli may be the cause of lymphatic drainage problems. Very successful SLN detection rates were obtained, even with the use of radiocolloid alone, in the Luminal A/B group in the present study.

The effects of breast cancer molecular subtypes on SLN or axillary metastases have been examined in many studies, but their relation to the technical success in SLN detection has not been sufficiently examined. The results of our study with a relatively small number of patients lead us to conclude SLN detection technique and tumor biology as Her2 (+) or TN are significant deterministic factors on SLN detection success rate. More prospective studies with higher numbers of patients are needed in this regard.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Oncology Hospital (AOH-211/2006).

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

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Original Article

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Impact of Personality Traits, Anxiety, Depression and Hopelessness Levels on Quality of Life in the Patients with Breast Cancer

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ABSTRACT

Objective: The aim of this study was to investigate the impacts of personality traits, anxiety, depression and hopelessness levels on quality of life in the patients with breast cancer.

Materials and methods: The study was performed on 90 patients diagnosed with breast cancer and 90 healthy women. Sociodemographic and Clinical Data Collection Form designed by us, Beck Hopelessness Scale (BHS), Beck Anxiety Scale (BAS), Beck Depression Scale (BDS), Eysenck Personality Inventory (EPI) and Quality of Life Scale–Short Form (SF-36) were administered to patients and to control group.

Results: The patients with breast cancer were found to indicate higher levels of anxiety and depression, lower levels of quality of life, and higher scores of personality inventory subscales as compared to the healthy control group. In the patient group, it was identified that the quality of life subscale scores were found to be negatively correlated with anxiety, depression, hopelessness and neurotic personality scores; there was a positive correlation between neurotic personality scores and depression, anxiety and hopelessness scores.

Conclusions: It can be concluded that the breast cancer patients with extraversion personality traits have lower levels of anxiety and depression, keeping their quality of life better, whereas the patients with higher neuroticism scores may have more impaired quality of life. Therefore, the psychiatric evaluation of the breast cancer patients during and after the treatment cannot be ruled out.

Keywords: Breast cancer, personality, anxiety, depression, quality of life

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Introduction

Diagnosis and treatment of breast cancer have considerable psychological influences on women (1). After the establishment of the diagnosis of breast cancer, fear of death, hopelessness and fears related to expected change of life, along with impaired quality of life due to treatment may give rise to negative perceptions in patients. Then, after primary treatment, fear of recurrence, changes in mood, increased

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sensitivity, uncertainty, sense of loss (e.g., fertility), body image disturbance, decrease in self-esteem, sexual problems, economic concerns, family-related issues and emotional problems may show up (2, 3). 20-35% of the female breast cancer patients experience psychiatric disorders such as depression and anxiety at any time of their disease regardless of the stage of the disease and treatment status (4). In their study on 222 patients with early stage breast cancer, Burgess et al. (5) found the prevalence of depressive and anxiety disorders as 33% at the time of diagnosis, 15% after one year from diagnosis, and 45% at the time of the diagnosis of recurrence, and indicated in the same study that frequency of anxiety and/or depression in female patients with breast cancer was two times more than the general female population. It was suggested that even 1 year after treatment, one third of the patients continued to have psychiatric disorder comorbidity (6). Recent studies have shown that psychiatric comorbidity is associated with increased symptom load, decreased adherence to therapy and impaired quality of life (7-9).

In addition to the signs of psychiatric disorders, the hypothesis that personality is associated with the risk of breast cancer and survival has been brought forward for a long time. A study conducted using Eysenck personality inventory (EPI) showed that the breast cancer patients with higher extraversion scores tended to have a lower risk of death. Findings available have demonstrated that personality has a considerable impact on development and progression of breast cancer (10). Neuroticism was defined as the personality trait most often associated with different aspects of breast cancer survival such as fatigue, lower level of quality of life and depression. It was also underlined that in addition to conservative therapy of breast cancer, personality, acceptability and neuroticism were important factors responsible for the emergence of depressive symptoms a year after surgical therapy (11). Moreover, in post-chemotherapy patients with breast cancer, cancer-related fatigue level was found to be correlated with psychoticism, extraversion/introversion, neuroticism and lie subscales of EPI (12). There are few studies on investigation of the relationship between personality traits and the quality of life in the patients with breast cancer. Thus, the present study was designed to explore the impacts of personality traits, anxiety, depression and hopelessness levels on quality of life in patients with breast cancer.

Materials and Methods

Subjects

This study incorporated 90 patients aged between 18 and 65 and diagnosed with breast cancer who presented to our hospital for outpatient and inpatient treatment and who gave written consent to take part in the study as well as a control group of 90 healthy subjects who were matched to the patient group by age and sex. Inclusion criteria for the patient group was set as follows: being aged between 18 and 65, being literate, accepting to take part in the study, having been diagnosed with breast cancer, being at stage 1, 2 or 3 of the disease at the time of study, having no other types of cancer, not having received for a period of at least 3 months any of combined therapies including radiotherapy and chemotherapy other than hormone therapy. Exclusion criteria included having mental retardation or any disorder associated with alcohol and substance use, having schizophrenia or any other psychotic disorder, having dementia or any other cognitive disorders, having any neurological diseases such as epilepsy, multiple sclerosis or Parkinson's disease, and having any systemic diseases that might lead to cognitive impairment. On the other hand, the control group was formed by healthy volunteers who were literate, aged between 18 and 65, and who agreed to participate in the study. This study was approved by the ethics committee of the İstanbul Bilim University.

Assessments

In the light of the clinical experience and literature review and considering the purposes of the study, both patient and control groups were administered semi-structured Sociodemographic and Clinical Data Collection Form, Beck Hopelessness Scale (BHS), Beck Anxiety Scale (BAS), Beck Depression Scale (BDS), Eysenck Personality Inventory (EPI) and Quality of Life Scale–Short Form (SF-36). The scales of the study were applied under the supervision of psychiatrists and psychologists.

Patient Follow-up Form (Sociodemographic and Clinical Data Collection Form): Having been filled in by the research physician, this form included questions relating to patient's age, sex, marital status, educational background, working status, smoking and alcohol habits, and medical history of every patient and her relatives.

Beck Hopelessness Scale (BHS): This scale was developed by Beck et al. Validity and reliability study for the Turkish version was conducted by Seber et al. (13). This instrument is designed to measure an individual's negative attitudes about the future (13). Subsequently, Dell further studied this scale, and obtained more comprehensive information on the scale's validity, reliability and factor structure. BHS is a 20-item inventory, being scored from 0 to 1. Higher total scores are indicative of higher levels of hopelessness (14).

Beck Anxiety Scale (BAS): This scale was developed by Beck et al. (15) in 1988 in response to the need for a scale that was able to distinguish anxiety from depression. It is designed to measure severity of anxiety symptoms experienced by individuals. It interrogates subjective anxiety and bodily symptoms. Consisting of 21 items and being scored from 0 to 3 as based on the Likert scaling, it is a self-report scale. Total scores range from 0 to 63. Higher total scores indicate more severe anxiety levels experienced by the subject. Validity and reliability study for Turkish version of this inventory was performed by Ulusoy et al. (16).

Beck Depression Scale (BDS): As a self-report inventory, BDS was designed was Beck in 1961 to measure emotional, cognitive, somatic and motivational components (17). The inventory consists of 21 items, two of which are oriented to emotions, eleven to cognitions, two to behaviors, five to physical symptoms, and one to interpersonal symptoms. It consists of 21 questions in total, each answer being scored on a scale value of 0, 1, 2, and 3, to obtain a score ranging from 0 to 63. As based on the total scores, 0–9 indicates no/minimal depression, 10–18 indicates mild depression, 19–29 indicates moderate depression, and 30–63 indicates severe depression. Used to detect the intensity of depressions, BDS was tested for its suitability to Turkish society by a validity and reliability study conducted by Hisli (18).

Eysenck Personality Inventory (EPI): This instrument allows for assessment and measurement of such dimensions of personality as neuroticism-stability, extraversion-introversion, psychoticism and lie in the context of Eysenck's personality theory. It is a self-report scale comprising of 24 yes/no items and 4 subscales. The validity and reliability of this instrument in Turkish language was tested by Karancı et al. (19) in 2007.

Table 1. Sociodemographic characteristics of the patient and control group

		Patient group N(%)	Control group N(%)	p
Age		50.43±7.45 (mean+SD)	50.28±7.11 (mean+SD)	0.886
Education status	Primary school	18(19.8)	56(53.8)	0.062
	High school	18(19.8)	28(26.9)	
	College	14(15.4)	8(7.7)	
	University	41(45.1)	12(11.5)	
Marital status	Single	39(42.9)	59(56.7)	0.455
	Married	52(57.1)	45(43.3)	
Working status	Housewife	56(61.5)	69(66.3)	0.456
	Working	35(38.5)	35(33.7)	

Mean±SD= mean±standard deviation; *: p<0.05

Table 2. Scale scores of the patient and control group

	Patient group N:90 (Mean±SD)	Control group N:90 (Mean±SD)	p
BDS	8.93±7.09	3.99±4.22	0.000*
BHS	4.80±3.62	3.82±4.0	0.088
BAS	13.94±10.18	5.38±5.43	0.000*
P-FUNC	26.59±3.12	73.61±21.09	0.000*
P-ROLE	7.3±1.2	26.92±21.21	0.000*
PAIN	9.45±2.46	77.34±22.7	0.000*
G-HEALTH	17.46±2.28	65.56±27.74	0.000*
LIVE	16.29±2.42	51.61±19.10	0.000*
S-FUNC	7.71±1.99	70.01±23.98	0.000*
E-ROLE	4.76±1.12	32.38±19.08	0.000*
M- HEALTH	25.90±3.02	67.93±15.78	0.000*
E-N	12.01±5.15	2.47±1.27	0.000*
E-E	11.81±3.97	2.72±1.83	0.000*
E-P	7.41±4.68	1.5±1.25	0.000*
E-L	12.10±4.41	3.38±1.68	0.000*

BDS: beck depression scale; BHS: beck hopelessness scale;
BAS: beck anxiety scale; P-FUNC: physical function;
P-ROLE: physical role weakness; G-HEALTH: general health perception;
LIVE: life; S-FUNC: social functioning; E- ROLE: emotional role;
M-HEALTH: mental health; E-N: eysenck neuroticism;
E-E: eysenck-extrovert; E-P: eysenck-psychotism; E-L: eysenck-lie;

Quality of Life Scale– Short Form (SF-36): This form is designed to measure quality of life among those with physical disease and psychiatric disorder, as well as healthy subjects. The form consists of 36 items and investigates eight dimensions of health: physical functioning, role limitations (arising from physical and emotional issues), social role functioning, mental health, vitality (energy), bodily pain and general health perceptions. As there is no standard total score, scores from eight sections are summed up (20). A validity and reliability study of the Turkish version of SF-36 has been conducted (21).

Statistical analysis

Statistical analyses were performed using Statistical Packages for the Social Sciences (SPSS) version 17 (SPSS Inc.; Chicago, IL, USA). Compatibility of the variables to normal distribution was assessed both visually (via histograms and probability graphs) and analytically (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics were illustrated using medians from frequency tables for non-normally distributed variables, whereas the variables with normal distribution were illustrated using means and standard deviations. Differences were compared with the help of one-way Analysis of Variance (ANOVA) test. Homogeneity of variances was evaluated by means of Leven's test. Any outcome for which the p–value was less than 0.05 was considered as being statistically significant. In cases where there existed significant differences between groups, Dunnett's test was used in doubles. In analysis of quantitative variables chi-square test was employed. Regarding the relations between BHS, BAS, BDS, EPI and SF-36 form, correlation coefficients and statistical significances were calculated with the help of Spearman test. Type-1 error rate for statistical significance was established as 5%.

Results

This study included 90 patients who were diagnosed with breast cancer and satisfied inclusion criteria, as well as 90 healthy women who matched the patient group in terms of age and sex. The mean age was 50.43±7.45 and 50.28±7.11 in the patient group and the control group, respectively. No statistically significant difference was identified between the patient group and the control group in terms of sociodemographic attributes, except smoking habits and bodily illness record in family history (p>0.05) (Table 1). While all the BAS, BDS scale scores and SF-36 and EPI subscale scores were statistically significantly different in the patient group (p<0.05), BHS demonstrated no statistically significant difference (p>0.05) (Table 2).

In consequence of the correlation analysis between BDS and SF-36 subscale scores in the patient group, a negative correlation was present between BDS scores and SF-36 subscales: physical functioning (r=-0.345, p=0.001), physical role difficulty (r=-0.431, p=0.000), pain

Table 3. Correlation results between the EPI, BDS, BAS, BHS levels and SF-36 subscales

		P-FUNC	P-ROLE	PAIN	G-HEALTH	LIVE	S-FUNC	E-ROLE	M-HEALTH
E-N	r	-.269*	-.189	-.270*	-.203	-.267*	-.170	-.288*	-.274*
	p	.010	.074	.010	.054	.011	.109	.006	.008
E-E	r	.084	.077	.153	.044	.217*	.191	.163	.312*
	p	.433	.471	.151	.681	.040	.071	.124	.003
E-P	r	.014	-.032	.018	.164	-.102	.063	.090	.158
	p	.899	.770	.868	.126	.345	.557	.405	.139
E-L	r	.034	.052	-.060	-.044	.127	-.049	-.017	-.095
	p	.753	.625	.574	.681	.234	.649	.870	.369
BDS	r	-.345*	-.431*	-.366*	-.457*	-.681*	-.248*	-.474*	-.626*
	p	.001	.000	.000	.000	.000	.019	.000	.000
BHS	r	-.201	-.375*	-.153	-.309*	-.410*	-.138	-.279*	-.158
	p	.057	.000	.149	.003	.000	.196	.008	.134
BAS	r	-.435*	-.285*	-.294*	-.275*	-.493*	-.143	-.307*	-.453*
	p	.000	ç007	.005	.009	.000	.180	.003	.000

*: p<0.05
EPI: eysenck personality inventory; E-N: eysenck neuroticism; E-E: eysenck extrovert; E-P: eysenck-psychoticism; E-L: eysenck-lie; BAS: beck anxiety scale; BDS: beck depression scale; BHS: beck hopelessness scale; SF-36: quality of life scale-short form; P-FUNC: physical function; P-ROLE: physical role weakness; PAIN: pain; G-HEALTH: general health perception; LIVE: life; S-FUNC: social functioning; E- ROLE: emotional role weakness; M-HEALTH: mental health

Table 4. Correlation results between EPI subscales and BDS, BAS, BHS scales

		BDÖ	BUÖ	BAÖ
E-N	r	.408*	.223*	.387*
	p	.000	.034	.000
E-E	r	-.257*	-.060	-.117
	p	.014	.573	.273
E-P	r	-.125	-.110	-.045
	p	.245	.308	.677
E-L	r	-.120	-.079	-.108
	p	.262	.461	.310

Mean±SD=Mean±Standard Deviation; *: p<0.05
EPI: eysenck personality inventory; E-N: eysenck neuroticism; E-E: eysenck extrovert; E-P: eysenck-psychoticism; E-L: eysenck-lie; BAS: beck anxiety scale; BDS: beck depression scale; BHS: beck hopelessness scale

(r=-0.366, p=0.000), general health perception (r=-0.457, p=0.000), vitality (r=-0.681, p=0.000), social functioning (r=-0.248, p=0.019), emotional role difficulty (r=-0.474, p=0.000) and mental health perception (r=-0.626, p=0.000) (p<0.05). The correlation test between BHS scores and SF-36 subscale scores revealed a negative correlation with physical role difficulty (r=-0,375, p=0.000), general health perception (r=-0.309, p=0.003), vitality (r=-0.410, p=0.000) and emotional role difficulty (r=-0.279, p=0.008) subscales (p<0.05). According to the correlation analysis between BAS and SF-36 subscale scores, BAS scores were identified to have been negatively correlated with physical functioning (r=-0.435, p=0.000), physical role difficulty (r=-0.285, p=0.007), pain (r=-0.294, p=0.005), general health perception (r=-0.275, p=0.009), vitality (r=-0.493, p=0.0009), emotional role difficulty (r=-0.307, p=0.003) and mental health perception (r=-0.453, p=0.000) (p<0.05). Results from the correlation test between EPI subscales and SF-36 subscale scores indicated that Eysenck neuroticism subscale was negatively correlated with physical functioning (r=-0.269, p=0.010), pain (r=-0.270, p=0.010), vitality (r=0.267, p=0.011), emotional role difficulty (r=-0.288, p=0.006) and mental health perception (r=-0.274, p=0.008) (p<0.05), while there was a positive correlation between Eysenck extraversion subscale and vitality (r=0.217, p=0.040), mental health perception (r=0.312, p=0.003) subscales of SF-36 (p<0.05) (Table 3). The correlation analysis between EPI subscale scores and BDS, BHS and BAS subscale scores demonstrated that a positive correlation was present between neuroticism subscale of Eysenck and BDS, BHS and BAS (r=0.408, p=0.000; r=0.223, p=0.034; r=0.387, p=0.000, respectively), whereas Eysenck extraversion subscale was negatively correlated with BDS (r=-0.257, p=0.014) (p<0.05) (Table 4).

Discussion and Conclusion

Breast cancer is one of the most prevalent types of cancer among women. It accounts for 33% of all cancer cases, and 20% of cancer-specific mortalities in women (22). In the patients with breast cancer, serious psychological issues may emerge due to the reasons such as uncertainty about success of therapy, physical symptoms, fear of recurrence and death, changes in gender identity, body image perception and sexual functions, difficulties in daily life activities, family-related problems and lack of emotional support (23-25). The most

common types of psychiatric disorders are depression and anxiety. The comorbidity of depression accompanying breast cancer is as high as 46%, and this rate is even higher within the first year following establishment of initial diagnosis (26). Besides even after 5th year of initial diagnosis, approximately 15% of the patients show depressive symptoms (5). Depressive disorder in the patients with breast cancer negatively affect psychosocial adaptation, deteriorating overall quality of life. This in turn reduces survival rates as a function of the decreased therapeutic suitability (27). A study designed to investigate the impact of disease-related factors and health-related quality of life on depressive symptoms showed that depressive symptoms affected physical well-being, social roles, emotional functions, pain, sleep disorders and vomiting (28). According to another study on health-related quality of life in the patients with breast cancer from the viewpoint of physical symptoms and signs of depression, depressive symptoms affected body image, sexual function, sexual drive and long-run future expectation with the combined impact of physical symptoms, which accounted for 57% of all depressive symptoms, mainly in four areas including arm, chest, hair and other side effects. In a study by Karakoyun et al. (9) on the women with breast cancer, it was reported that anxiety and depression put a negative impact on the quality of life and cancer fighting. In addition, social support and notably family support were reported to have reduced depressive symptoms and improved the quality of life (9, 29). Another study on the relationship between anxiety and quality of life in the patients with breast cancer showed that functional dimensions including physical, emotional, social and cognitive functions suffered from deterioration in the patients showing the signs of anxiety, and that a positive correlation was present between anxiety scores and body image, future expectations and sexual function (30). Cognitive attitudes such as hopelessness, desperation and lack of support were found to be associated with depression at a statistically significant level (31). In the context of the present study, all subgroups of anxiety, depression and quality of life scores were found to be statistically significantly different in the breast cancer group compared with the control group.

According to the correlation analyses between the quality of life and depressive symptoms in the patients with breast cancer, impaired functioning and quality of life as part of symptoms were shown to have affected depressive symptoms (32). Another similar study demonstrated that the quality of life was affected by depressive symptoms, negative body perception, hopelessness, negative associations to future expectations and somatic symptoms (33). It was also observed that in breast cancer patients with high levels of anxiety, physical and other functions remained in a bad state during and after treatment, and that the scores representing the sense of feeling emotionally good were considerably affected. In those with higher depressive scores, on the other hand, levels of functioning in physical, social and emotional dimensions were reported to be weak (34). In a similar vein, our study detected a negative correlation between anxiety and depression scores and the dimensions of quality of life: physical functioning, physical role difficulty, pain, general health perception, vitality, emotional role difficulty and mental health perception.

Limited number of studies have been made on whether there are differences in the patients with breast cancer and the general population in terms of personality traits. However, it has been addressed that personality traits might affect traumatic life events such as cancer (35). It is neuroticism, one of the sub-dimensions of Eysenck personality inventory, which has been considered the most associated personality trait with different aspects of breast cancer survival such as fatigue, lower level of quality of life and depression (11). Former studies showed no difference between the patients with breast cancer and the control group in terms of extraversion and neuroticism, while some researchers emphasized that breast cancer patients indicated higher psychoticism scores compared with the control group (35). Yet, cancer survivors including breast cancer survivors were reported to have lower levels of psychoticism, which was associated with lower levels of quality of life (36). In keeping with this, another study suggested that the psychoticism was a personality trait which was the predictor of depression and bodily symptoms in breast cancer survivors (35). The present study found that neuroticism, psychoticism, extraversion and lie subscale scores were higher than those of the control group. Furthermore, neuroticism scores were found to be positively correlated with depression and anxiety scores. The patients with higher extraversion scores demonstrated lower depressions scores.

Researches on the relationship between personality traits and the quality of life reported that the patients with higher neuroticism scores had poorer quality of life (37). Emotional and total scores of the quality of life were found to be lowered by personality disorder, depressive disorder, having weaker coping mechanisms, and keeping self-accusatory personality traits in the forefront (38). The patients with breast cancer indicating the signs of personality disorders were found to be under a higher risk of having post-treatment generalized anxiety disorder and major depressive disorder (39). Moreover, a weak correlation was detected between the power of scale scores indicative of absence of affective behaviors or lack of confidence in subjective sensations and development of breast cancer (40). In our study, on the other hand, neuroticism scores were found to be negatively correlated with following subscales of the quality of life: physical functioning, pain, vitality, emotional role difficulty and mental health perception, whereas extraversion subscale of Eysenck personality inventory showed a positive correlation with SF-36 vitality, social functioning and mental health perception subscales. In other words, neurotic breast cancer patients showing signs of anxiety and concern experienced a greater deterioration in quality of life. Besides that, certain subscales of the quality of life were positively affected in the extroverted patients who were social and open to verbal contact and communication.

In the present study, anxiety and depression levels of the patients with breast cancer were found to be higher compared with the control group. The patients with higher neurotic personality, anxiety and depression scores were found to have poorer quality of life. Moreover, it was observed that extraverted patients had better quality of life scores, with lower levels of anxiety and depression. Considering both findings from this study and the current literature, it can be concluded that the patients with extraversion personality traits have lower levels of anxiety and depression, keeping their quality of life better, whereas the patients with neurotic personality traits may show symptoms of anxiety and depression, with poorer quality of life. In view of the fact that psychiatric diseases may develop in patients with breast cancer due to their personality traits, which may in turn affect their quality of life, careful psychiatric characterization of these patients and enabling them to receive psychiatric assistance where necessary would definitely put a positive impact on treatment processes.

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

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Original Article

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Scoring Idiopathic Granulomatous Mastitis: An Effective System for Predicting Recurrence?

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ABSTRACT

Objective: Idiopathic granulomatous mastitis is a breast disease without a definitive etiology. There are no definitive classifications, scoring systems or certitudes. The aim of this study is to define the factors related to the recurrence and design a scoring system.

Material and Methods: Patients who were admitted to the general surgery department with symptoms of granulomatous mastitis were evaluated by ultrasonography and underwent antibiotic therapy. Granulomatous mastitis is diagnosed by core biopsy and treated with steroid therapy. Patients without improvement underwent surgery and were included in the study. In total, 53 patients were included in the study. There were 8 recurrent cases. Factors related with recurrences were defined.

Results: Number of births over 2, duration of lactation more than 18 months, body mass index greater than 31, having fistula in physical examination, abscess collection in ultrasonographic examination, and luminal inflammation score over 2 were scored as 1. Severity score in recurrent cases were 5.1±0.6 whereas 1.9±1.0 in nonrecurrent cases.

Conclusion: Granulomatous mastitis score is a tool targeted at predicting the risk of recurrences. The patients with these factors are more prone for recurrences.

Keywords: Granulomatous mastitis, recurrence, risk factors, surgery

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Introduction

Idiopathic granulomatous mastitis (IGM) is a rarely seen inflammatory breast disease without a clearly elucidated etiology. The etiological factors underlying this disease are currently unclear, although a localized autoimmune inflammatory response to retained and extravasated fat- and protein-rich (milk) secretions in the duct has been implicated in its pathogenesis (1). Pregnancy, parity and lactation are considered as risk factors in the pathogenesis of IGM (2-4). Usual presentations of IGM are breast mass, sinus formations and abscesses (1, 2). Entities that should be considered in the differential diagnosis of IGM are malignancies, lactation mastitis, sarcoidosis and tuberculosis (5). The diagnosis of IGM requires a multidisciplinary approach, incorporating clinical, radiological, microbiological and pathological findings.

The best practices for the treatment of IGM are controversial. Conservative treatment such as the use of antibiotics or corticosteroids, or wide excision of the affected tissue have been utilized for treatment (6, 7). Currently, there is no consensus for an ideal way to match a treatment modality to a patient. The current approach to IGM treatment consists of short-term antibiotics, followed by histological confirmation with a core needle biopsy. Following pathological confirmation, the decision to proceed with steroid therapy and/or surgical excision is then left to the clinician (8). The decision criteria for steroid treatment, dose of steroid or the duration of steroid treatment are uncertain. Since successful treatment of IGM is considered to be healing of the current disease, with no recurrences in patient follow-up, the lack of an objective, reproducible severity score for IGM makes it harder for the clinician to stratify patients according to recurrence risk and make an informed decision on the appropriate treatment modality.

In this study, we aimed to develop a combined clinical and histological scoring system to determine the severity of IGM that would assist the clinician in determining the recurrence risk based on factors that were implicated in a higher risk of disease recurrence.

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Material and Methods

This study was approved by local ethic committee. Patient information was collected from the hospital database and pathology reports. As being a retrospective study, inform consent was not received from the patients.

Diagnosis and patient selection

A total of 110 patients admitted to our surgery department between January, 2008 and January, 2014 for mastitis, who were then confirmed histologically as IGM, were included in this retrospective study. The study was approved by local ethics committee. Our study method incorporated a multidisciplinary approach in elucidating suspected risk factors for IGM. Hospital records of histologically confirmed IGM patients were reviewed and data on clinical and imaging features were collected. Pathological specimens were re-examined. In our center, patients referred to the Department of General Surgery with mastitis were evaluated in order to differentiate other possible causes. In the case of an ongoing sinus discharge, special stains (Gram, Ziehl-Neelsen, periodic acid Schiff) were used to identify possible organisms in the discharge fluid. Ampicillim-sulbactam (2x1g P.O.) was given to all patients for 10 days. In cases where clinical improvement was absent or minimal, a core biopsy was obtained for the diagnosis of IGM. Patients diagnosed as IGM then underwent corticosteroid treatment (Methylprednisolone (Prednol, Mustafa Nevzat, İstanbul, Turkey)) (30mg/day) for 3 months. The dose of steroid was obtained from the previous studies (1, 3, 7). At the end of the treatment, the dose was tapered in 3 days. In cases of incomplete response, disease relapse and problems with patient compliance with the medical regimen, surgical excision was offered to the patient as a treatment choice. The patients who accepted surgical excision were included in our study. The patients were followed up for at least 2 years (2-8 years) for the relapse symptoms after surgery. The patients were then divided into two groups: Group I, composed of patients with recurrences and Group II, composed of patients without recurrences within 2 years of follow-up.

Severity score factor estimation:

Recent studies about IGM were consulted in order to identify suspected risk factors for disease recurrence (9-14). Information about hyperprolactinemia, coexisting Sjögren's syndrome, length of breast feeding period, contraception usage, parity, age at first birth, smoking habits, age, Body Mass Index (BMI), habitual choices in breastfeeding, and bra-wearing habits were obtained from the patients' files. Existence of fistula, hyperemia, and breast pain were noted. Data on the existence of abscess, diameter of breast lesions and the existence of multifocality were obtained from radiological examination reports. Pathological specimens were re-evaluated in order to score the severity and extent of inflammation separately for interstitial, perilobular, intraepithelial and luminal compartments. Inflammation was scored visually using a modified version of the histopathological classification system developed by Nickel et al (15).

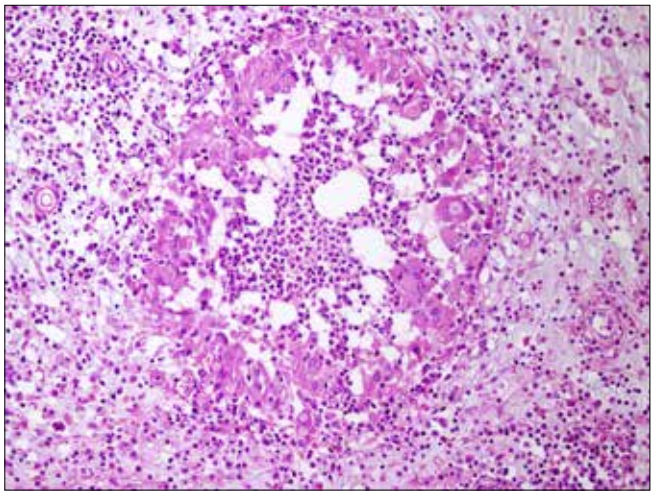

Figure 1. Sections of the breast biopsy showed replacement of breast tissue by a diffuse inflammatory infiltrate of histiocytes and lymphocytes with some epithelioid multi-nucleated giant histiocytes (a. hematoxylin and eosin, x100; b. hematoxylin and eosin, x200)

Lactation period, BMI and number of births were analysed by ROC (Receiver Operating Characteristics) (Med Calc Software, Belgium). Having BMI over 31 BMI (ROC area 0.8±0.04), lactation period over 18 months (ROC area 0.9±0.05), and giving births three or more (ROC area 0.83±0.08) were found to be significant. For this reason, these factors were accepted as risk factors.

Obtained data was evaluated by SPSS 15.00 (SPSS Inc. Chicago, IL, USA). Nonparametric comparisons were performed by chi-square and parametric comparisons were performed by Student's t-test. p values <0.05 were accepted as significant.

Results

Within the initial group of 110 patients who presented with IGM, we were able to obtain complete clinical, radiological, pathological and follow-up data for 63 patients, who were then included in our study. The mean age of the patients was 38.6±8.4 (23-61). There were 8 recurrences (%12.6) in our study, who underwent subsequent re-excision of affected tissue. None of the patients in our study had Sjögren's syndrome or hyperprolactinemia. In order to determine the risk factors, we compared the patients with and without recurrences. Contraception usage, parity, age of first birth, affected breast (left or right), bilateral disease, bra-wearing habits or smoking didn't show any significant difference between two groups (p>0.05). The existence of hyperemia or breast pain was again not significant (p>0.05). The ultrasonographic mean diameters of the breast lesions in two groups or multifocality were also not statistically different (p>0.05). As a pathological risk factor, interstitial, perilobular, or intraepithelial inflammation scores didn't show a statistically significant difference between patient groups. Histopathological examination revealed features of granulomatous process with multi-nucleated giant cells, epithelioid cells and macrophages forming non-caseating granulomas around lobules; neither evidence of malignancy nor any specific organism was found. Absence of caseous necrosis was marked in the granuloma, which was surrounded by micro abscesses. Most of the cases (22 of the 33 cases) in our study had mixed inflammation and 11 cases had chronic inflammation. Interstitial inflammation was observed in all cases but perilobular, luminal and intraepithelial inflammation were less frequent. Granuloma formation was not observed in 4 cases, but intense mixed inflammation was seen with marked histiocytic infiltration. Abscess formation was observed in %45.4 of cases in our study. (Figure 1-3)

The number of births, duration of lactation, BMI, presence of fistulas, abscess formation detected in ultrasonographic examination and luminal inflammation were found to be significantly different between recurring and non-recurring patients (Table 1). After defining the

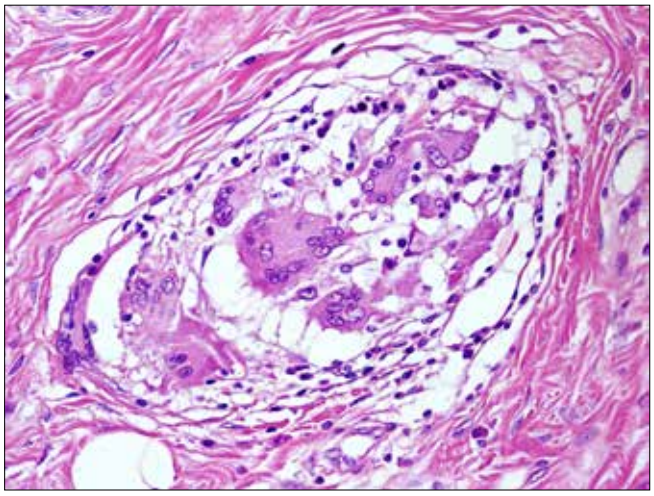

Figure 2. High power (hematoxylin and eosin, x400) picture showing giant cells in granulomatous mastitis

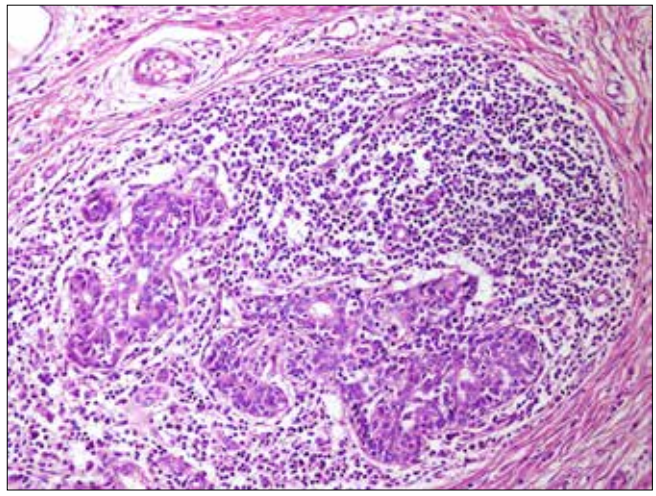

Figure 3. Biopsy specimen shows perilobular chronic inflammation (hematoxylin and eosin, x200)

Table 1. Significant differences between recurrent and nonrecurrent cases

	Mean Age, Years	Mean BMI, kg/m²	Mean Number of Births	Mean Duration of lactation	Existence of fistula, n (%)	Existence of abscess, n (%)	Luminal inflammation, n (%)	Mean GM score	Total
No recurrence	38.4±8.7	28.4±4.8	2.0±0.8	15,6±9.2	8 (%14.5)	9 (%16.3)	0 (%0)	2.1±0.9	55
Recurrence	40.1±6.2	33.8±1.5	3.8±1.4	33.6±10.9	6 (%75)	7 (%87.5)	5 (%62.5)	5.0±0.7	8
p	0.6	0.003	0.001	0.001	0.001	0.001	0.001	0.001	

BMI: body mass index; GM: granulomatous mastitis

Table 2. Idiopathic Granulomatous Mastitis Score

Granulomatous mastitis score	0	1
Number of Births, n	<2	3≤
Duration of Lactation, months	<18 months	18 months ≤
BMI (kg/m²)	<31	31≤
Luminal inflammation score higher than 2.	Absent	Present
Existence of fistula	Absent	Present
Abscess collection in USG examination	Absent	Present

BMI: body mass index; USG: ultrasonography

factors which are significantly different between recurrence and nonrecurrence cases, we classified risk factors into a) patient related, b) discovered during physical examination, c) radiological and d) pathological. Number of births higher than 2, breastfeeding for more than 18 months, and a BMI higher than 30 were implicated as patient related risk factors for recurrence. The presence of fistulas was regarded as a clinical risk factor whereas abscess formation detected by ultrasonographic examination was accepted as a radiological risk factor. A luminal inflammation score higher than 2 was noted to be a pathological risk factor. The presence of each risk factor then was given a score of 1 and a total risk score was then calculated for each patient (Table 2). The mean idiopathic granulomatous mastitis scores of patients with and without recurrence were 5.1 and 1.9, respectively. The difference was statistically significant (p<0.001) (Table 1).

Discussion and Conclusion

Idiopathic granulomatous mastitis is a benign aseptic inflammatory disease of the breast without an obvious etiology. The disease is seen in young- or middle-aged women within a couple years after giving birth. The disease is localized to the breast without any systemic findings (12, 13). Non-puerperal breast secretion has been implicated in the pathogenesis of IGM. An autoimmune reaction against secretions that leak to the interstitium from breast lobules is the suspected mechanism of the disease. This reaction may lead to mass formation, hyper-

emia, pain, ulceration, abscess, and fistulae. Possible correlation with a number of agents, such as local irritants, viruses, mycotic and parasitic infections, tuberculosis, hyperprolactinemia, diabetes mellitus, smoking, and alpha-1 antitrypsin deficiency have been postulated, but have never been clearly demonstrated to be related with the severity or recurrence of the disease. (9-14, 16, 17).

There is no ideal definitive treatment strategy for IGM. Oral contraceptives, surgery, antibiotics and immunosuppressive treatment are the preferred treatments for the IGM (1, 3, 16, 18). The failure of the treatment is the recurrence of IGM and the excision of breast tissue ensures negative margins for IGM with low recurrence rates. However, the surgical treatment has unfavorable cosmetic results. On the other hand, some cases can be easily treated by oral corticosteroids (3). For this reason, several studies prefer step-by-step treatment for the management as starting with antibiotics and then steroids and finally surgery (3, 6, 17). The response to the preferred treatment probably depends on the severity of the IGM. Severity of IGM result in recurrences after preferred treatment. For this reason, several studies have been performed for the risk factors for recurrences (10, 11, 13, 14). In our study, we evaluated the risk factors for IGM recurrences and selected these factors for defining the severity score for IGM.

Microbiological agents such as Corynebacterium spp. have been implicated in the pathogenesis of IGM. Previous studies have shown that antibiotic treatment can be beneficial in the management of the disease (16, 17). However, we did not consider these factors for severity assessment due to a limited number of studies and insufficient evidence linking specific microbiological agents to IGM (19, 20). On the other hand, contact with wild household mice has been shown to be a risk factor for IGM in the study of Oltean HN et al. (10). This correlation might be related to infectious agents, but Asoglu O et al. (6) in a separate study, was not able to identify any microbiologic agents with sufficient evidence to be causal for IGM. In our study, patients received oral antibiotics in order to suppress possible infectious mastitis, which might complicate underlying IGM and to treat any possible infectious mastitis before the steroid treatment as is recommended in the study of Omranipour R et al. (8).

Oral contraceptive (OCS) use, which is another factor that has been implicated in IGM, has been known to increase breast secretions. However, in our study, no significant association was detected between OCS use and IGM. The association between IGM and OCS use has been reported to range between 0%-42% in a number of previous studies (13). Similarly, the association between IGM and smoking habits is not significant in recent studies, ranging between 0%-50% (10). This wide range, coupled with the limited number of cases in the aforementioned studies, is not sufficient to accept smoking and OCS use as a risk factor.

Parity has also been considered in the aetiology of IGM, in which hormonal changes (hyperprolactinemia) after birth lead to increased breast secretions and subsequent inflammation. After giving birth, breast lobules switch to a secretory phenotype and ductules are found to be dilated. This is hypothesized to be an initiating factor for IGM (1). Similarly, almost all studies on subject to date have reported parity to be associated with IGM (10). As the number of births increase, the incidence of IGM is also increased as reported in a previous study (10). In our study, all patients had a history of parity and recurrent cases had a high number of births (Table 2). For this reason, we included multiparity as a factor in our risk assessment.

During lactation, breast tissue secretes milk as long as breastfeeding continues. Breast lobules under prolactin stimulation secrete protein-rich liquid, and the ducts remain dilated. It has been reported that prolonged breastfeeding might result in long-term distention of acini and ducts; this may facilitate rupture of these structures, resulting in a granulomatous inflammatory response (21). Several studies have reported an association between breastfeeding and IGM (14, 16, 17). Non-alternating breast feeding was a risk factor for IGM in previous studies (10, 13, 21). Continuing milk secretion without breastfeeding leads to milk stasis and predisposes to mastitis in that breast. However, it is hard to define and measure the breastfeeding habits of each participant, since breastfeeding practices often vary considerably between mothers. In our study, breastfeeding for longer than 18 months was implicated as a risk factor for IGM recurrence.

Body mass index is used as an indicator of obesity in a population. Although BMI has not been previously evaluated in IGM patients, we realized that obese patients with IGM had high recurrence rates. Even though BMI is not an indicator of breast volume or adipose tissue extent, inflammation has been known to spread faster through adipose tissue (22). This might lead to a more complicated IGM presentation in obese patients and render such patients more prone to recurrence.

Patients with IGM generally present with a breast mass that is initially difficult to differentiate from breast cancer. Breast imaging should be performed for differential diagnosis. As most of the patients are younger than 40 years of age, mammary ultrasound is the preferred method. Inhomogeneous hypoechogenicity with internal hypoechoic tubular lesions might suggest the possibility of IGM (23). Increased parenchymal echo pattern, with multiple irregular hypoechoic masses with finger-like projections, are the most reported ultrasonographic findings in patients with IGM (23). Abscess formation can also be detected via USG and have been reported at varying rates (6%-%31) (1, 23). Abscess formation is a complication of IGM and might be a factor for severity of IGM. In our study, the ultrasonographic detection of a breast abscess increased the recurrence rate (Table 2).

Inflammation in IGM starts around lobules (24). As the disease progresses, this inflammation reaches duct lumens and the interstitium (25). In our study, it was seen that recurrent cases with dominant fistula formation had prominent luminal inflammation. It might be postulated that severe inflammation, starting from breast acini, can progress into the breast ducts, causing eventual rupture of ducts and acini with a subsequent heavy interstitial inflammatory reaction against milk proteins and cellular fragments, which can then organize into abscesses that fistulize to the skin. As a result, the extent and severity of luminal inflammation are reflected as a higher recurrence rate for the patient.

Granulomatous mastitis is one of the more distressing breast diseases in women. There is no current consensus on the etiology, classification and severity of the disease (26). This is the first study, to our knowledge, to explore the utility of a combined clinical, radiological and pathological risk factor score in determining IGM recurrence risk. One of the main problems facing the clinician in managing IGM patients is the lack of an established disease classification system for IGM, which makes it harder for the clinician to stratify patients according to recurrence risk and make an informed decision on the appropriate treatment modality. This study might help establish a baseline for future studies that aim to establish a definitive classification system for IGM. By using this severity scoring system, the treatment can be designed

in a precise manner. Low-risk patients can be treated without surgery; on the other hand, high-risk patients might be referred directly to the surgical treatment without wasting time with medical therapy. Steroid treatment in high-risk patients not only results in delay of the treatment but also has risks of steroid complications. This scoring system does not only guide the treatment but may also aid presenting the patient in medical language.

The relatively low number of patients with recurrences is the main limitation of our study, which also rendered our data unsuitable for regression analysis. As the IGM is rare disease, multi-center studies are needed in order to overcome this limitation. Being a retrospective type is the other limitation for our study. But there is no bias nor irrelevant data in our study. Although this study is retrospective, pathological specimens are re-evaluated for the new scoring system. As being the first, we hope that prospective studies performed in future would overcome these limitations.

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

Informed Consent: Written informed consent was not recieved due to the retrospective natüre of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - T.U.Y.; Design - T.U.Y., B.G.; Supervision - Z.U.; Resources - M.A.B., B.E., S.D.; Materials - M.A.B., B.E., S.D.; Data Collection and/or Processing - T.U.Y., S.A.G., B.G.; Analysis and/or Interpretation - M.A.B., S.A.G.; Writing Manuscript - T.U.Y., B.G., S.A.G.; Critical Review - S.A.G., Z.U.

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Original Article

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Sentinel Lymph Node Metastasis in Invasive Lobular Carcinoma of the Breast

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ABSTRACT

Objective: Invasive lobular carcinoma (ILC) of the breast makes up 5 to 15 percent of all invasive breast cancers. It has distinctive clinical and histopathological features when compared to invasive ductal carcinoma (IDC). This study intends to describe factors influencing sentinel lymph node (SLN) positivity in patients with "pure" ILC.

Materials and Methods: Data of 105 patients, who were treated at a tertiary oncology center, with lobular carcinoma of the breast that were subjected to SLN biopsy was probed retrospectively. Patients were categorized as ≤60 and >60 years of age, positive or negative for estrogen receptor and progesterone, tumor grade I, II and III, Ki67≤15% and >30%, lymphovascular invasion presence and the presence of multicentricity and multifocality.

Results: Mean age at the time of diagnosis was 52 (38-81). Mean tumor size was 2.7 cm (0.7-13cm). Univariate analyses revealed a significant relationship between tumor size (≤2 cm vs >2cm) and metastasis in the SLN. This relation kept its significance in multivariate analyses. (p=0.013).

Conclusion: With so many different characteristics from IDC, ILC is mostly a uniform tumor. In this study, tumor size was the only independent clinical parameter that was found related to SLN metastases.

Keywords: Invasive lobular carcinoma, sentinel lymph node, metastasis

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Introduction

Invasive lobular carcinoma (ILC) of the breast makes up 5 to 15 percent of all invasive breast cancers (1). It has distinctive clinical and histopathological features when compared to invasive ductal carcinoma (IDC), which is the most common type of breast cancer by far. Patients having ILC are likely to be older and to have larger primary tumors at presentation than patients with IDC (2, 3). Sentinel lymph node (SLN) biopsy is the standard care for clinically node-negative IDC and ILC, although there are very few reports on factors influencing the status of SLN for each tumor subtype in the literature (4-6). This study intends to describe factors influencing SLN positivity in patients with "pure" ILC.

Materials and Methods

Data of 105 patients, who were treated at a tertiary oncology center, with "pure" lobular carcinoma of the breast that were subjected to SLN biopsy was probed retrospectively. One hundred and six SLN biopsies were performed (one patient with bilateral invasive lobular carcinoma). Primary surgery was mastectomy or breast conserving surgery according to the standard staging of the tumor. SLN(s) was/were sent for frozen section analysis, sliced at 2 mm intervals, and examined under hematoxylin and eosin stain and with immunohistochemistry (IHC) where needed. For those with metastatic (positive) nodes, full axillary lymph node dissection (ALND), involving levels I and II were carried out during the same surgical session. Patients having tumors with invasive ductal component (mixed type) were excluded. Preoperatively detected axillary lymph node involvement was also a reason for exclusion, where a complete axillary dissection was performed straight away.

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The preoperative systemic staging was done performing a routine physical examination, abdominal ultrasound, whole body bone scintigraphy, and computerized tomography (CT), if necessary. Mammography (MG) and breast ultrasound were the standards for breast imaging; magnetic resonance imaging (MRI) was performed if needed. Tc-labeled radioactive tracer and methylene blue dye were used together to identify SLN(s). The following was noted for each patient: age, tumor size, tumor grade, multicentricity and multifocality of the tumor, estrogen receptor (ER) and progesterone receptor (PR) receptor status, c-erb-B2 positivity, Ki67 expression, presence of lymphovascular invasion (LVI), dissected SLN number, positive SLN number, number of SLN with micrometastasis, number of SLN with extracapsular invasion (ECI), number of patients whom ALND was performed, number of dissected lymph nodes during ALND, number of positive lymph nodes after ALND and non-SLN positivity.

Patients were categorized as ≤60 and >60 years of age, positive or negative for ER and PR, tumor grade I, II and III, Ki67 ≤15% and >30%, having LVI presence and the presence of multicentricity and multifocality.

Institutional Review Board approval of Ankara Oncology Research and Training 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, undertaken by any of the authors, involving human participants or animals.

Statistical Analyses

Data was presented as mean, percentage and range and comparison of the data between groups was made with Chi-square and Fisher's exact tests. For predictive factors affecting SLN positivity, multivariate analysis/Cox proportional hazard regression model was used. A statistical software package for Windows was used for analysis. A p value of ≤0.05 was sought for significance.

Results

Mean age at the time of diagnosis was 52 (38-81). Mean tumor size was 2.7 cm (0.7-13 cm). When compared with preoperatively performed imaging studies, actual tumor size in the pathological specimen was greater in 70 patients (66%). According to TNM classification, 36 patients had T_1 (34%) tumors. Most patients had grade II tumors (n=74, 69.8%). ER and PR positivity were present in 98.1% and 87.7% of the patients respectively, whereas c-erb-B2 was positive in only 2.8%. Sixty-nine patients had Ki67 expression lower than 15% compared to 17 who had greater than 30%. LVI was seen in 4.7% of patients. A mean of 2 SLNs was dissected (1-8) in which SLN positivity was found in 29.2% of cases. Primary surgery was a mastectomy in 73 patients, 6 with concurrent reconstruction with a silicone implant. The incidence of non-SLN positivity was 12.3%. Characteristics of the patients and their tumors are given in Table 1.

Table 1. Patient and tumor characteristics

Parameter	n (%)
Age in years	
Mean (range)	52±11.3 (38-81)
Tumor size in cm	
Mean (range)	2.7±1.9 (0.7-13)
T classification	
<2cm (T1)	36 (34)
2-5cm (T2)	53 (50)
>5cm (T3)	17 (15)
Bloom-Richardson grade	
I	13 (12.3)
II	74 (69.8)
III	19 (17.9)
Receptor status	
ER (+)	104 (98.1)
PR (+)	93 (87.7)
c-erb-B2 (+++)	3 (2.8)
Ki67<15	69 (65.1)
Multicentricity/multifocality (+)	27 (25.5)
Lymphovascular invasion	5 (4.7)
Sentinel lymph node dissected	
Mean (interval)	2.4±1.4 (1-8)
Patients with metastatic sentinel lymph node	31 (29.2)
Extracapsular invasion (+)	6 (5.7)
Micrometastatic sentinel lymph node	3 (2.8)
Number of metastatic sentinel lymph node	1.4±0.9 (1-5)
Patients who underwent axillary dissection	30
Patients having non-sentinel metastasis	13 (12.3)
Axillary Dissection	
Mean dissected lymph node	17.3±6.3 (7-31)
Mean metastatic lymph node	2 (1-16)
Surgical procedure	
Mastectomy	73 (68.9)
Breast-conserving surgery	33 (31.1)

ER: estrogen receptor; PR: progesterone resceptor

Table 2. Multivariate test result for tumor size

Tumor size	Patients=n	Patients with positive sentinel lymph node=n (%)	p value	Odds ratio (95% confidence interval)
≤2cm	36	5 (13.8)		
>2cm	70	26 (37.1)	0.013	3.66 (1.26-10.59)

Univariate analysis revealed no significant difference in SLN status when the age of the patient, tumor grade, hormonal receptor status, Ki67 expression, multifocality and multicentricity of the primary tumor and LVI were compared. The only parameter found to be related to SLN positivity was the tumor size. As a multivariate test, logistic regression analysis demonstrated the persistence of significance of the tumor size (Table 2).

Discussion and Conclusion

Invasive lobular carcinoma is a completely different entity with its unique clinical and pathological features. It arises from the same organ as IDC, and its treatment and outcomes are almost the same as the stage-matched IDC. However, all things in between seem to differ. Clinically, ILC presents more commonly in advanced ages and the breast mass is greater in size at the time of diagnosis (2, 3, 7). In this study mean age of patients with ILC was 52, and mean pathological tumor size was 2.7 cm (T2 tumor). Immunhistochemically, ILC tend to have a high incidence of ER and/or PR expression, making it a more "female" cancer. The c-erb-b2 expression is quite uncommon, and proliferation index, illustrated by Ki67 stain, is lower. These cells are also reluctant to make lymphovascular invasion (8-12). Patients in this study represented a high ER and PR expression, 98.1% and 87.7% respectively. Only 2 (1.8%) were hormone receptor negative. Three tumors (2.8%) were overexpressing c-erb-B2 and only one patient had a triple-negative tumor. Most of the patients (65%) represented a very low proliferation index. LVI in the primary tumor was detected in only five (4.7%).

Pathologically, tumor cells with lobular origin are small and mostly round shaped (9). The most important feature of these cells is the lack of E-cadherin expression, a protein responsible for intercellular adhesion. Therefore, cells are noncohesive and display a single layer arrangement in the tissue (8, 9, 11). This feature may be the reason that preoperative imaging studies underestimated the primary tumor size in 70 cases (66%) in this study. Scattered cells through the breast tissue could explain the high rates of multicentricity/multifocality accompanying ILC (13, 14). One in every four patients had a multicentric/multifocal tumor in this study, presumably contributing to the size mismeasurement encountered with preoperative imaging. A different clinical impact of the loss of cohesion in between ILC cells was underlined by Topps at al. in their study, which interpreted the sensitivity of ultrasound-guided fine needle aspiration biopsy for axillary nodes of ILC patients. The scattered metastasis in the lymph node caused an inferior sensitivity rate for ILC (53.6% vs 98.4% for IDC) (7).

Although conflicting results exist on axillary metastasis of ILC, most studies conclude that they appear to be more in number and greater in size than IDC (7, 12). Almost 30% of clinically node negative cases in this analysis had positive SLN and 43.3% (n=13) of those had additional lymph node involvement in the non-SLNs. One of the few studies comparing axillary node involvement and the ratio of metastatic/dissected axillary nodes between ILC and IDC reported a mean of 4.2 vs 2.12 lymph node metastasis for the grade-matched ILC and IDC respectively (12). With similar grade distribution (grade II>grade III>grade I), our report revealed a mean metastatic axillary node of 2.5. The ratio of metastatic/dissected axillary nodes was 0.13 in this study in contrast to 0.37 in the report above.

Age, tumor size, tumor grade, hormone receptor status, Ki67 value, the presence of multicentricity/multifocality and LVI were tested for possible predictors of SLN positivity. Univariate analyses revealed a significant relationship between tumor size (≤2cm vs >2cm) and metastasis in the SLN. This correlation kept its significance in multivariate analyses with an Odds ratio of 3.66 (p=0.013) (Table 2). The other factors failed to correlate with SLN involvement. The only paper found in English language literature, focusing on predictive factors of sentinel node metastasis in patients with ILC, was by Grube et al. (15). They found tumor size and age of the patient were predictive factors of metastasis to SLN(s). However, their SLN positivity was 50%, mean age of the patients was more than 60, and their study lacks multivariate analysis of their data.

There are few reports that have investigated the predictive factors for SLN positivity among patients with IDC. Tumor size, vascular invasion, age, menopause status, tumor size, pathological type, hormone receptor status, and tumor location in the Upper outher quadrant were found to have a significant impact on SLN metastasis for IDC (4-6).

With so many different characteristics from IDC, ILC is mostly a uniform tumor. Unexceptionally good prognostic features such as hormone receptor positivity, low expression of c-erb-B2, and low proliferative activity do not seem to correlate with axillary lymph node status. In this study, tumor size was the only independent clinical parameter that was found to be correlated to SLN involvement.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Oncology Research and Training Hospital (2016/114).

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

Peer-review: Externally peer-reviewed.

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

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Original Article

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Validity and Reliability of Turkish Male Breast Self-Examination Instrument

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ABSTRACT

Objective: This study aims to measure the validity and reliability of Turkish male breast self-examination (MBSE) instrument.

Materials and Methods: The methodological study was performed in 2016 at Ege University, Faculty of Nursing, İzmir, Turkey. The MBSE includes ten steps. For validity studies, face validity, content validity, and construct validity (exploratory factor analysis) were done. For reliability study, Kuder Richardson was calculated.

Results: The content validity index was found to be 0.94. Kendall W coefficient was 0.80 (p=0.551). The total variance explained by the two factors was found to be 63.24%. Kuder Richardson 21 was done for reliability study and found to be 0.97 for the instrument. The final instrument included 10 steps and two stages.

Conclusions: The Turkish version of MBSE is a valid and reliable instrument for early diagnose. The MBSE can be used in Turkish speaking countries and cultures with two stages and 10 steps.

Keywords: Male breast cancer, male breast self-examination, Turkish, validity, reliability

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Introduction

Breast cancer is a malignant condition starting in the breast cells. Although it is thought to be a disease typical in women, about 1% of all breast cancers appears in men (1, 2). While it occurs in men aged 65 years on average, its incidence shows a peak at the ages of 68-71 years (3, 4). It has been reported men perceive that breast cancer is an illness that occurs mainly later in life (5). In Britain, 350-400 men can be diagnosed as breast cancer every year (6). According to data from International Association of Cancer Records, breast cancer is responsible for 0.37% of all cancers in men (3). Turkey Cancer Statistics reported that, the age-standardized breast cancer rate distribution in males is 0.8 in 2014 (World Standard Population, 100,000 people) (7). It has been reported in the literature that the incidence of male breast cancer is increasing (1, 4). However males had lower risk factor awareness than women across breast cancer (8). Based on data from American National Cancer Institute, Stang and Thomsen (9) reported that the incidence of breast cancer decreased in women but increased in men. It is also noted that the incidence increased from 0.86 to 1.8 for every 100.000 men (9).

The most important risk factor for male breast cancer is hormonal changes. Among them are changes in estrogen and testosterone. In a study in Sweden in 1988, the risk was found to increase by eight times in men working in manufacture of estrogen containing cream and soap. The strongest condition related to breast cancer is Klinefelter syndrome. In this syndrome, one X chromosome is added to XY chromosomes available in males and causes an increase in breast cancer risk (4, 10, 11). Obesity is another important risk factor since it increases estrogen-testosterone levels in males. It is stated that breast cancer risk rises by two fold in males with a body mass index of 30 and higher. Other risk factors are exposure to radiation, exposure to long-term high temperatures and hereditary transmission. It has been reported that 5-30% of all male breast cancer cases have a family history of breast cancer (10).

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Since male breast cancer is a rare tumor and can be mistaken for other conditions such as gynecomastia, there can be a delay in its recognition and can have an advanced stage when diagnosed. This has a negative effect on its prognosis (2, 3). The rate of survival is lower in males with breast cancer than in females. Five-year survival recorded in Britain is 80.8% in males and 86.6% in females (6). Delayed diagnosis of breast cancer in males has been attributed to their disregard for symptoms and lack of knowledge about the issue in the society (2). Therefore, the public awareness should be raised and people should be informed about male breast cancer in order to prevent delays in diagnosis and treatment. Awareness of symptoms of the disease and elimination of waste of time in referral to hospital will increase rates of early diagnosis. The National Comprehensive Cancer Network (12) recommends breast self- examination (BSE) as a primary prevention method and clinical breast examination (CBE) twice a year for males at risk of breast cancer. Not only women but also men should carry out a breast self-examination minimum once a month at the age of 18 years onwards. However, according to research, males do not have sufficient information about breast self-examination and believe that this examination and the disease are common among females (13, 14). The main reason for this is that brochures and education and counseling programs about breast cancer are directed towards women rather than men (15, 16). However, in view of an increase in the male breast cancer incidence, it is clear that breast self-examination is important for males. It is stated that this examination is a reasonable and practical method for early diagnosis of breast cancer in developing countries (11). Expressing specific steps in this examination in a clear and understandable way plays an important role in its acceptance and implementation. Al-Naggar and Al-Naggar (11) created Male Breast Self-Examination (MBSE) composed of two sections and ten steps illustrated by pictures. The MBSE is a simple early detection method which can be made easily by men. There have not been any studies on breast self-examination or a practical instrument to be used in early diagnosis of breast cancer in Turkish men. It will be useful to adapt an instrument directed towards promotion of breast self-examination and to spread its use in order to achieve primary prevention of male breast cancer in Turkey. Therefore, the aim of this study was to adapt MBSE into Turkish and to test its validity and reliability.

Material and Methods

Research Design: This study was performed to measure the validity and reliability of Turkish version of MBSE instruments as the methodological study.

Study sample

The methodological study was performed between May and June in 2016 in İzmir /Turkey. The sample included 112 male nursing students. All male students participated in this study. The sample met the criteria by Cochran formula more than 10 times of questionnaire items (17). Aim of the study was shared and verbal consents of participants were obtained. Ethical approval to conduct the study was provided by the Ethics Committee of Medical Faculty.

Instrument

The original MBSE instrument was developed by Al-Naggar and Al-Naggar in English and the Malay language in 2012 (11). It takes ten minutes to perform MBSE. The MBSE steps are performed in two stages: in the supine position and in front of the mirror. Men should be explained how they should examine their nipples and areolas and how they should perform steps of the examination to detect both painless and painful, firm masses with irregular outlines, changes in appearance of nipples and retraction, ulceration and hemorrhagic discharge in nipples.

Translation of MBSE

In this study, a six-step translation method was adopted as required in international methodological recommendations about linguistic and cultural adaptation of measurement instruments (18,19) (Figure 1). Following the standardized way, the MBSE was translated for linguistic validation content validity index (CVI) was determined. CVI was determined by using Davis technique (17, 20). According to this technique, items are evaluated on a four-point scale: (a) "The item is appropriate", (b) "The item should be slightly revised", (c) "The item should be revised extensively" and (d) "The item is inappropriate". The number of experts marking the options (a) and (b) is divided by the total number of experts to calculate CVI for an item. The cut-off value for this index is considered as 0.80 (17, 20).

Consistency between expert opinions was analyzed with a non-parametric test Kendall W analysis (17). The measurement instrument can be considered valid; first its linguistic validity should be achieved. According to this, differences in concepts and expressions between adapted and original versions of the instrument should be minimized, the adapted version should be meaningful and standardized in accordance with norms of target languages, the nature of the original instrument should not be changed or changes to be made should be minimized (21, 22). Expert opinion was requested from ten academicians having specializations in surgical nursing, obstetrics and gynecology nursing, medical nursing, public health nursing and fundamentals of nursing to achieve content validity of the Turkish version of MBSE. Expert opinion was asked to evaluate the instrument in terms of contents of the steps, appropriateness of the language for the Turkish population, clarity and understandability. MBSE was piloted on 30 university students for clarity and understandability. These participants were not included in the larger study.

Validity

Factor analysis with varimax rotation was used for defining the construct validity of the instrument. Eigenvalues higher than 1.0 and factor loadings at least 0.30 was used as a criteria to fitting structure and

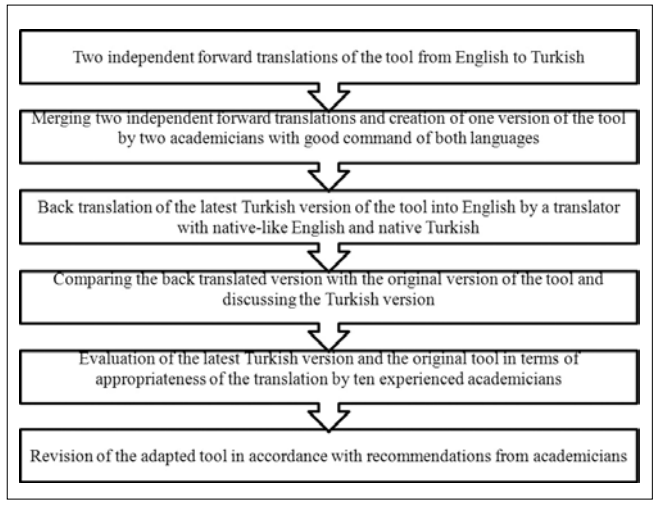

Figure 1. Standardized translation process of the MBSE

the correct number of factors (17, 21). Before conducting the factor analysis of the instrument, Kaiser Meyer Olkin (KMO) and Bartlett's test were used to calculate whether the sample was large enough to perform satisfactory factor analysis.

Reliability

In the present study, Guttman scaling was used to a set of binary questions answered by a set of subjects. The goal of the analysis is to derive a single dimension that can be used to position both the questions and the subjects (17). The instrument has "Yes (1)", "No (0)" answers to a set of steps that increase in specificity. For defining the reliability of the current study, Kuder Richardson 21 was used. The values above 0.8 showed good convergence was used as the criteria in the current study (17, 22).

Ethical approach: Aim of the study was shared and verbal consents of participants were obtained. Ethical approval to conduct the study was provided by the Ethics Committee of Medical Faculty (8 May 2016; number 21). Permission was obtained by email from Al-Naggar and Al-Naggar to use the MBSE instruments in this study.

Statistical analysis

The data was analyzed by using analytics software (SPSS 17.0). Inferential statistical methods (exploratory factor analysis, Kuder Richardson 21) were used.

Results

The mean age of students was 19.10±2.05 and all of them were male. Of all the participants', 26.8%, 31.2%, 25% and 17% were attending 1st year, 2nd year, 3rd year, 4th year class respectively. Seven point one percent of the participants reported there were female breast cancers in their first degree relatives. None of the participants reported that there was male breast cancer in their first degree relatives. To adapt the form into Turkish, it was translated from English to Turkish independently by two English teachers whose native languages are Turkish and two academicians having knowledge of breast cancer and living abroad for some time in their life. After that, the researchers evaluated translations of each item and created a single Turkish version of the instrument. At this stage, some revisions in words and sentences were made in terms of appropriateness of the language, meaning and concepts. The steps translated into Turkish were back translated into English by a linguist having good command of both languages. The original form and the Turkish version of the form were compared. Expert opinions about the translations of the steps were exemplified below (Table 1).

In accordance with feedbacks received, the expressions were revised and the final version of the instrument was created. The cut-off value of CVI was considered as 0.80 and none of the items were found to have a lower CVI. For all ten steps CVI was 0.94 and the Kendall W coefficient was 0.80 (p=0.551).

The pilot study allowed testing clarity, understandability and functionality of the steps in practice. No suggestions were made by the participants and the version of the instrument used in the pilot study was considered as its final version. It is presented in Appendix 1.

For construct validity of the instrument, the factor analysis was done using 10 steps. The Kaiser Meyer Olkin was obtained at 0.87 (Bartlett's test 2728.2, p<0.001). Two significant factors were identified for the MBSE. The largest factor emerging after Varimax rotation is 28.31% of variance, 25.63% of the second factor variance. The total variance explained by the two factors was found to be 63.24%. Factor loading of variables was shown at Table 2.

Six steps of MBSE for lying down check Kuder Richardson 21 was found to be 0.91. Four steps of MBSE for in front of mirror check Kuder Richardson 21 was found to be 0.83. Kuder Richardson 21 was found to be 0.97 for the 10 steps instrument (Table 3).

Table 1. Translations of authors and experts about the of steps of MBSE

Translations of authors	Translations of experts
Stage 1- Lying down	
Lie on your back with a pillow under your right shoulder	Lie on your back with a pillow under your right shoulder
Check your right breast by using tips of your three middle fingers of your left hand	Examine your right breast by using your three middle fingers of your left hand
Press your fingers without raising them from your skin by using mild, moderate and extreme pressure in the circular manner	Apply mild, moderate and extreme pressure in a circular manner without raising your fingers from your skin
Follow an upward and downward route with your fingers	Assess the whole breast tissue from the top to the bottom of your breast with your fingers
Check tissues under and above your clavicle and your armpits and feel changes	Feel changes in your armpits by checking tissues under and above your clavicle
Repeat the same steps with your right hand on your left breast	Repeat the same steps by using your right hand on your left breast
Stage 2- In front of mirror	
Keep your arms by your sides	Keep your arms aligning with your hips
Keep your arms on your head	Keep your arms on your head
Press your hands to your hips and stretch your breast muscles	Press your hands on your hips and stretch your breast muscles
Bend forward with your hands towards your hips	Put your hands on your hips and bend forward

MBSE: male breast self-examination

Table 2. Rotated factor analysis of the MBSE instrument

Factor 1, Lying down	Factor 2, In front of mirror
Step1 0.97	Step7 0.97
Step2 0.97	Step8 0.97
Step3 0.97	Step9 0.97
Step4 0.96	Step10 0.97
Step5 0.96	
Step6 0.96	
Eigen value	
10.71	8.64
Variance explained	
28.31	25.63

MBSE: male breast self-examination
N: 112, Steps/Items: 10

Table 3. Internal consistency determine: Kuder Richardson for factors

Factors	Number and Quantity of phrases	Kuder Richardson 21 (n=112)
First factor: Lying down	6 (1,2,3,4,5,6)	0.91
Second factor: In front of mirror	4 (7,8,9,10)	0.83
Total	10	0.97

Discussion and Conclusion

One important technical aspect of a measurement instrument is its validity in addition to its reliability (23). It shows whether a instrument really measures a variable thought to be measured by a researcher. In other words, it indicates what a instrument measures and how accurate measurements it makes (21, 24, 25). Although the ability of a instrument to be valid depends on its reliability, a reliable instrument without validity is not very important in practice (22). The issue of validity is related to the question whether researchers can measure a variable they think that they do (21).

The aim of the validity analysis made in the present study was to have a group of experts examine whether steps of MBSE really represent what they are supposed to measure and to create a complete instrument composed of meaningful items. Content validity is a measure based on judgments of experts. There are no objective criteria which ensure sufficiency of the content of a scale (20, 21). MBSE was sent to ten experts with different specializations for evaluation of its content. The experts were asked to evaluate each item of the instrument in terms of their content, linguistic appropriateness for Turkish population, clarity and understandability (22, 23). In view of the CVI of 0.80 recommended by Polit et al. (22) for content validity, the CVI of 0.94 obtained for all the items in the present study shows a consistency between opinions of the experts. Validity refers to the degree to which a variable has been measured. The most frequently preferred methods for evaluation of validity of a scale are content validity and construct validity (22, 24). Consensus between experts as a result of their evaluation of understandability and appropriateness of items in a instrument is considered as an indication of content validity of that instrument (17, 22). In the present study, Kendall W concordance test was performed to analyze content validity of MBSE. According to the test results, there was consensus between the experts (Kendall W=0.80, p=0.551) and the items were appropriate for Turkish culture and represented what was supposed to be measured.

In the present study, the final version of the MBSE instrument included 10 steps and two factors. After the factor analysis, six steps were observed in factor 1 "Lying down" check. Factor 2 "In front of mirror" includes four steps. These two factors were found similar with the original MBSE instrument (11). In the analysis of the basic components applied to the scale, two factors were obtained. The sampling adequacy calculated as KMO value in the study was found to be 0.87 and it implies that the sample size is perfect for factor analysis (17). The total variance explained by the two factors was found to be 63.24%. In this study, the Turkish MBSE instrument fully coincides with the original structure and conforms to the conceptually desired sub-dimensions. Kuder Richardson for the instrument was measured 0.97 and found excellent level of internal consistency (17, 21).

In conclusion, the final Turkish MBSE instrument included ten steps and two stages. The instrument is a valid and reliable for early detection of breast cancer in male. This instrument helps men to examine themselves and it could be used to improve men health in Turkey. The MBSE can be used in Turkish speaking countries and cultures.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ege University (08.05.2016/21).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Ö.E., İ.G.; Design - Ö.E., İ.G.; Supervision - Ö.E., İ.G.; Resources - Ö.E., İ.G.; Materials - Ö.E., İ.G.; Data Collection and/or Processing - Ö.E., İ.G.; Analysis and/or Interpretation - Ö.E., İ.G.; Literature Search - Ö.E., İ.G.; Writing Manuscript - Ö.E., İ.G.; Critical Review - Ö.E., İ.G.

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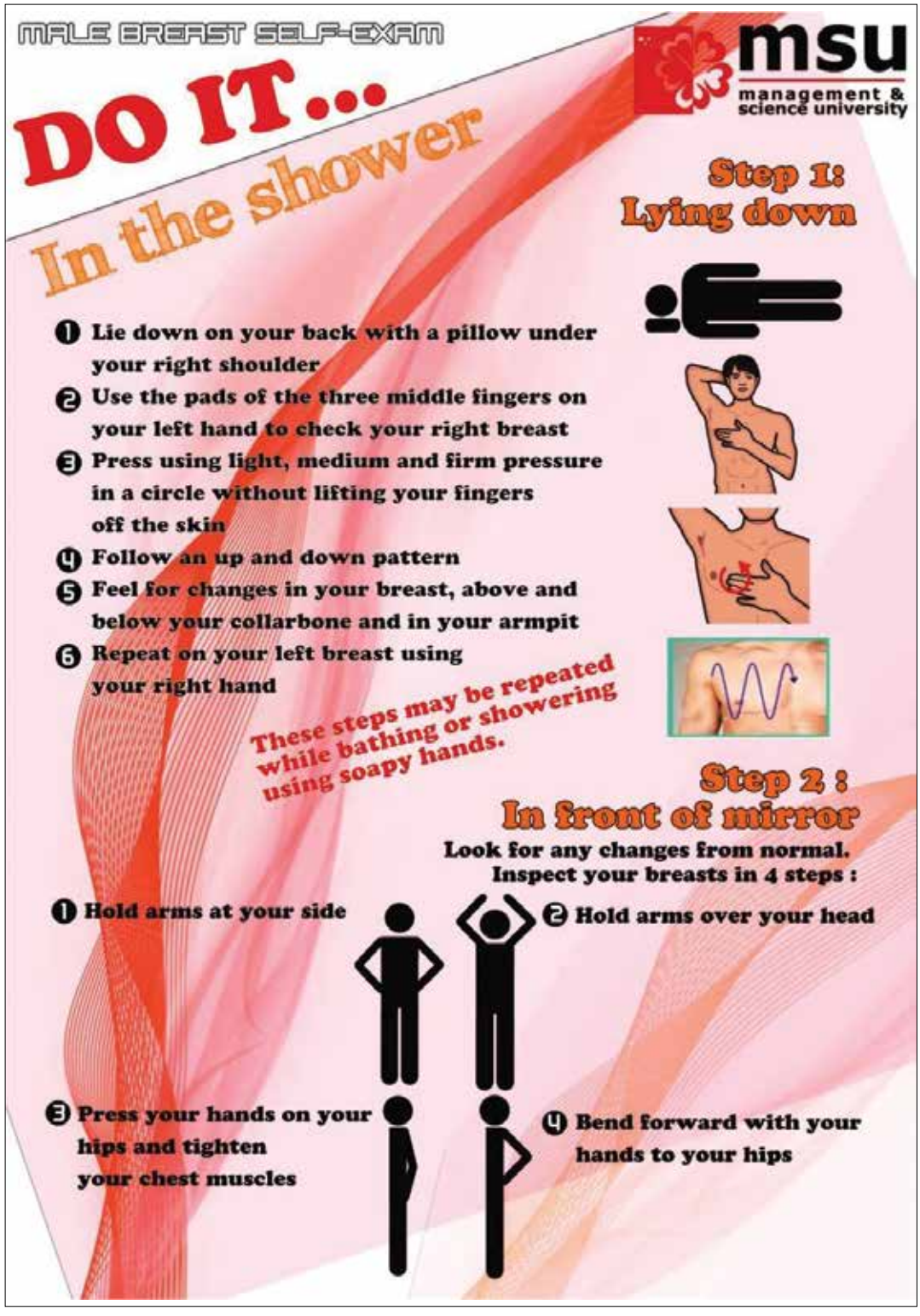
appendix1


MALE BREAST SELF-EXAM
DO IT...
In the shower
msu
management & science university
Step 1:
Lying down
1 Lie down on your back with a pillow under your right shoulder
2 Use the pads of the three middle fingers on your left hand to check your right breast
3 Press using light, medium and firm pressure in a circle without lifting your fingers off the skin
4 Follow an up and down pattern
5 Feel for changes in your breast, above and below your collarbone and in your armpit
6 Repeat on your left breast using your right hand
These steps may be repeated while bathing or showering using soapy hands.
Step 2 :
In front of mirror
Look for any changes from normal.
Inspect your breasts in 4 steps :
1 Hold arms at your side
2 Hold arms over your head
3 Press your hands on your hips and tighten your chest muscles
4 Bend forward with your hands to your hips

Case Report

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Encapsulated Papillary Carcinoma in A Man with Gynecomastia: Ultrasonography, Mammography and Magnetic Resonance Imaging Features with Pathologic Correlation

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ABSTRACT

Male breast cancer is an uncommon disease that constitutes 1% of all breast cancers and encapsulated papillary carcinoma (EPC) is a rare subtype of malignant male diseases. Gynecomastia is the most common disease of the male breast. We report a 63-year-old male patient with EPC accompanied by gynecomastia that was diagnosed and treated at our breast center. Mammography showed an oval-shaped dense mass with circumscribed margins on the ground of nodular gynecomastia. On ultrasonographic exam, we saw a well-circumscribed complex mass with a solid component which was vascular on Doppler ultrasonography. Magnetic resonance imaging revealed a complex cystic mass containing solid components. Dynamic images showed enhancement of the cystic mass wall and mural components. Tumor stage was evaluated as T2N0. The lesion's histologic examination and immunohistochemical analysis by showing no myoepithelial layer revealed an encapsulated papillary carcinoma. To our knowledge, this is the first case report which describes MR imaging findings of male breast encapsulated papillary cancer.

Keywords: Encapsulated papillary carcinoma, intracystic papillary carcinoma, male, gynecomastia, magnetic resonance imaging

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Introduction

Male breast cancer accounts for 1% of all breast cancers and 0.17% of all male cancers (1). The papillary variant of breast cancer represents 3 to 5% of cases in men, which is more common than women representing 1 to 2% of cases (2). Based on recent immunohistochemical studies, intracystic papillary carcinoma is called encapsulated papillary carcinoma (EPC) (3). Imaging findings of EPC in women have been reported in the literature many times (4-7). Mammography (MG) and ultrasonography (US) findings of male EPC was reported in a few case reports (8-10). However, to our knowledge, magnetic resonance (MR) imaging features of EPC in a male patient has been described in only one case which was an incomplete assessment (11). We report MG, US and MR imaging findings of a 63-year-old male patient with bilateral gynecomastia and a right subareolar palpable mass. This is the second case report of male breast encapsulated papillary cancer that included MR imaging features.

Case Presentation

A 63-year-old male who had a 1.5-year history of a mass located just below his right areolar region. He was admitted to our clinic because the mass has recently grown painless. There were no risk factors of breast cancer in his history. He did not have any systemic illness or drug usage history; routine blood and urine tests were normal. His BMI was 24. On physical examination, a 2 cm mobile mass was palpated in the right subareolar region. No skin abnormality was noted on inspection. Axillary examination was unremarkable. Bilateral craniocaudal and mediolateral oblique MG demonstrated an ellipsoidal nodular density under bilateral areolas considered as gynecomastia. These nodular appearances were evaluated as nodular gynecomastia. The right MG also showed an oval-shaped dens mass with circumscribed margins adjacent to gynecomastia (Figure 1). On US, we found a 23x19 mm well-circumscribed, predominantly cystic mas with solid components that evaluated as complex lesion. Increased blood flow was present within the solid components on Doppler US (Figure 2). Hypoechoic area compared to regional fat tissue that represented fibroglandular enlargement compatible with gynecomastia was seen on US in both breasts. MR images revealed a cir-

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Figure 1. (a-d). Bilateral craniocaudal and mediolateral oblique MG demonstrated nodular gynecomastia (stars). Oval-shaped dense mass with posterior-inferior circumscribed margins adjacent to gynecomastia on the right breast (arrows)

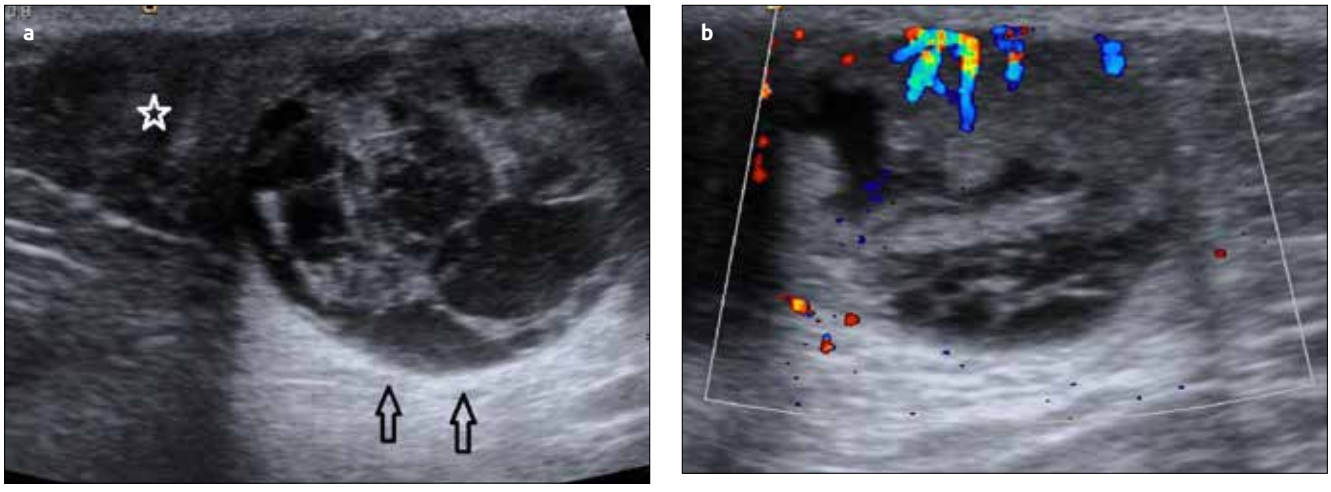

Figure 2. (a-b). US demonstrated hypoechoic glandular structure compatible with gynecomastia (star) and well-circumscribed mass shows predominantly cystic with solid components-thick septations that evaluated as complex lesion. Posterior acoustic enhancement was seen (stars) (a). On Doppler US, blood flow was seen in the solid components (b)

cumscribed hypointense mass and bilateral hypointense parenchyma on pre-contrast T1-weighted sequences. Axial T2-weighted images revealed complex mass containing hypointense solid components and hyperintense cystic component. Axial T1-weighted contrast-enhanced subtraction images revealed enhancement of the cystic mass wall and solid components. Sagittal post-contrast images showed a circumscribed complex mass with a cystic component (star) and markedly enhancing wall and solid nodules (Type III kinetic curve/suggestive of malignancy-not illustrated) (Figure 3). The lesion was reported as intracystic mass with a preliminary diagnosis of papillary carcinoma. Core needle biopsy was performed under US guidance. Histopathologically, the lesion had few papillary folds and was filled with uniform tumoral cells. Immunohistochemical analysis also confirmed no myoepithelial cells were stained with p40 in the lesion. So the final pathological diagnosis was EPC (Figure 4). Simple mastectomy was performed with axillary sentinel lymph node sampling. The size of the specimen was 15 cm and the tumor size was 2.5 cm. All 4 sentinel lymph nodes were negative. Receptor status was ER: 90% and PR:90%. The tumor cells were moderately differentiated (grade 2) and tumor stage was reported as T2N0. Written informed consent was obtained from the patient.

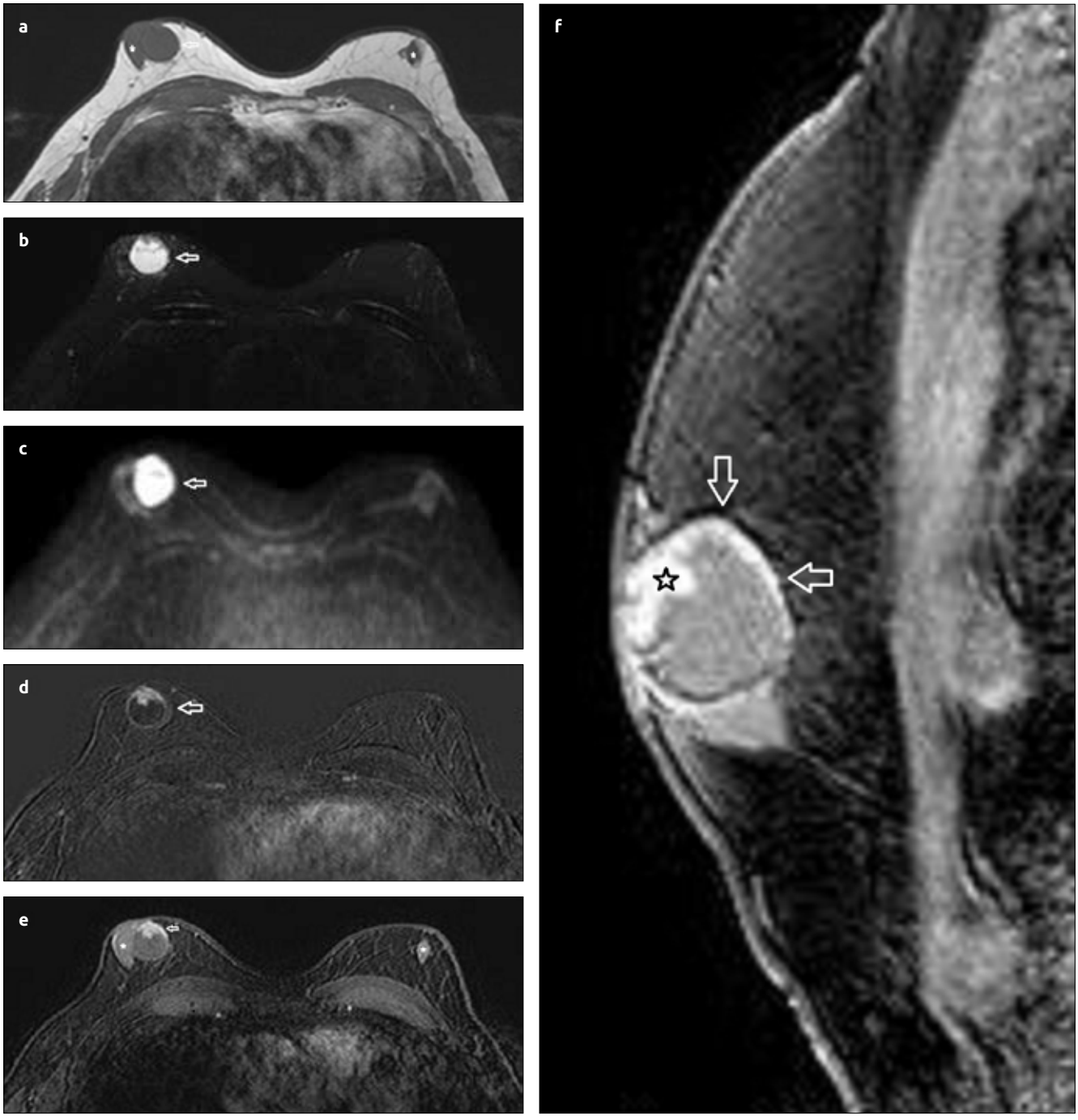

Figure 3. (a-f). a) MR images revealed a circumscribed hypointense mass (arrow) and bilateral hypointense parenchyma (stars) on pre-contrast T1-weighted image (a). Hyperintense complex cystic mass containing hypointense solid component (arrow) was seen on axial T2-weighted image (b). In diffusion-weighted image, the mass shows high signal intensity (c). Axial T1-weighted contrast-enhanced subtraction image showed enhancement of walls of cystic mass and solid nodules (d). Axial post-contrast T1-weighted gadolinium-enhanced image showed mass (arrow) and glandular appearance compatible with gynecomastia (stars) (e). Sagittal post-contrast image showed a circumscribed complex mass with a cystic component and marked enhancing solid nodules (arrows) and peripheral wall (star) (f)

Discussion and Conclusion

Encapsulated papillary carcinoma is a localized, encysted kind of papillary ductal cancer that surrounded by a fibrous capsule found within a dilated duct. EPC may be asymptomatic or present with a bloody nipple discharge or palpable mass. Many cases were also described in the male population in the literature, (12). The average age of EPC is higher than the other types of breast cancer, being 65-year old (13). Gynecomastia is quite common in male breast. In our patient, cancer and gynecomastia was diagnosed at the same time. Gynecomastia is not an independent risk factor for male breast cancer; most of the time, it presents concurrently with relative estrogen excess associated clinical conditions. Usually, this tumor can Show benign MG findings as a well-circumscribed, round or oval mass. However, true diagnosis of EPC can be made by adding US. US was absolutely necessary to evaluate internal structure of this

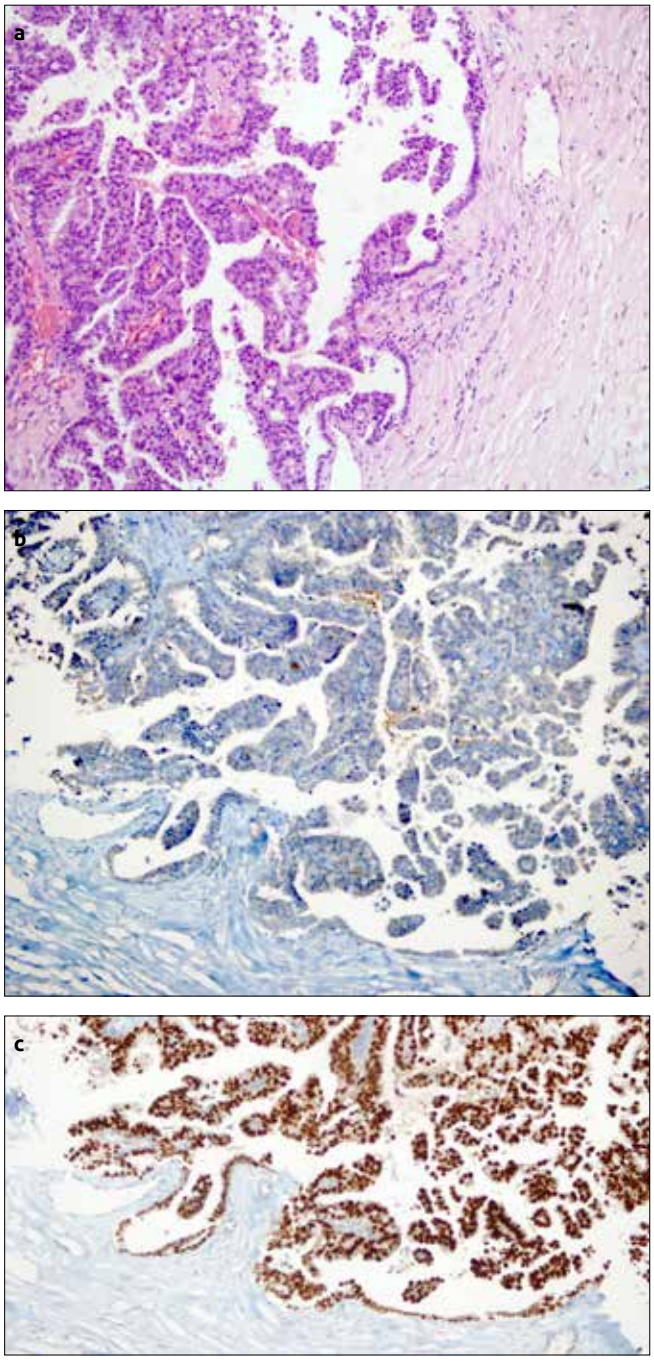

Figure 4. (a-c). Papillary configuration of the lesion within capsule (H&E, x20, original magnification) (a).
No myoepithelial cells stained with p40 in the lesion (p40, x20, original magnification) (b). ER positivity is high in the lesion (ER, x20, original magnification) (c)

mass which typically reveals complex appearance that includes a cystic area with solid components originating from the wall of the cyst.

Magnetic resonance imaging can give additional information about the morphological features and the local extension of the mass for preoperative mapping (14, 15). At MR imaging, round or oval mass with circumscribed margins has typical heterogeneous internal composition with solid nodules of intermediate signal intensity and also depends on the cystic component. EPC shows strongly enhancing cyst wall and solid nodules on post-contrast images. Differentiating EPC from intracystic papilloma is difficult, however MR imaging can guide us by showing the types of the kinetic curves of the solid nodules that demonstrate the presence of cancer (15). Even pathologically, EPC can be misdiagnosed as intraductal papilloma especially in small biopsies. Showing presence of myoepithelial layer is enough to give a diagnosis of intraductal papilloma. The recommended treatment is surgical excision with negative margins. Sentinel lymph node biopsy is recommended when tumor shows clinical N0 as usual breast cancer.

In conclusion, EPC in male breast is an extremely rare entity; however, cystic lesions in men should be worked up as potentially malignant lesions. MG and US together provide valuable information to direct us to the correct diagnosis. MR imaging of EPC in male breast has similar features as in female breast. Round or oval shape with predominantly circumscribed margins and the complex appearance of solid and cystic components are the specific features of EPC on US and MR imaging. Absence of myoepithelial cell layer by immunohistochemical study is significant for pathologic diagnosis.

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

Peer-review: Externally peer-reviewed

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

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