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REVIEW

ORIGINAL ARTICLES

Turkish Federation of Breast Diseases Societies

European Journal of Breast Health is the official journal of the **Turkish Federation of Breast Diseases Societies**

Société Internacionale de Sénologie | Senologic International Society

Global Federation of Breast Healthcare Societies

SIS is the official supporter of the European Journal of Breast Health

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European Journal of Breast Health

European Journal of Breast Health

Aims and Scope

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

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

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

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

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

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

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

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 conforms with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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European Journal of Breast Health

Instructions to Authors

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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).

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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.

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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
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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
Current Opinion	300	No abstract	5	No tables	No media

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

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.

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

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. All authors should be listed if an article has six or less authors; it should not be represented by "et al." in articles. Arabic numbers in parentheses. References published in PubMed should have a PMID: xxxxxx at the end of it, which should be stated in parenthesis. The reference styles for different types of publications are presented in the following examples.

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

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

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

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

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

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

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

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

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

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European Journal of Breast Health

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Review

Eur J Breast Health 2021; 17(2): 86-94
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New Frontiers for Fairer Breast Cancer Care in a Globalized World

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ABSTRACT

In early 2020, the book "Breast cancer: Global Quality Care" was published by Oxford University Press. In the year since then, publications, interviews (by ecancer), presentations, webinars, and virtual congress have been organized to disseminate further the main message of the project: "A call for Fairer Breast Cancer Care for all Women in a Globalized World." Special attention is paid to increasing the "value-based healthcare" putting the patient in the center of the care pathway and sharing information on high-quality integrated breast cancer care. Specific recommendations are made considering the local resource facilities. The multidisciplinary breast conference is considered "the jewel in the crown" of the integrated practice unit, connecting multiple specializations and functions concerned with patients with breast cancer. Management and coordination of medical expertise, facilities, and their interfaces are highly recommended. The participation of two world-leading cancer research programs, the CONCORD program and Breast Health Global Initiative, in this project has been particularly important. The project is continuously under review with feedback from the faculty. The future plan is to arrive at an open-access publication that is freely available to all interested people. This project is designed to help ease the burden and suffering of women with breast cancer across the globe.

Keywords: Quality, global health, breast cancer, innovation, value

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Key Points

- Strategic planning for global breast cancer control requires an active surveillance of breast cancer incidence, stage at presentation, and survival through population-based cancer registries.
- The maintenance of cancer registries requires a political will, legislative action, and financial stability to sustain their critical activities over time.
- Improved breast cancer outcome is best achieved through systematic approaches such as prevention, early detection, prompt diagnosis, and effective cancer management, where coordinated multidisciplinary teamwork is pivotal to success.
- Value-based healthcare used patient-centric care models, through which an evidence-based, resource-appropriate care pathway defines the optimal-quality integrated clinical practice.
- A value-based price threshold can guide the allocation of limited resources to achieve high-quality care.
- The regulation should ensure that cancer diagnostic and treatment innovations enter the market because of not only their potential benefit but also their demonstrated comparative cost-effectiveness. Decisions should not be based only on the results of traditional randomized controlled trials, but they should also include real-world data from population-based cancer registries and other sources.
- Breast cancer early detection through clinical downstaging is a prerequisite to mammographic screening.
- Governments must ensure that their health system is equitable and has the features required by human rights.

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Introduction (Video 1)

VideoLink1:https://www.youtube.com/watch?v=XDXBRtQQM68

In early 2020, the book "Breast Cancer: Global Quality Care" was published by Oxford University Press (1) (Figure 1). In August 2020, the article "Breast Cancer: Global Quality Care, Optimizing Care Delivery with Existing Financial and Personnel Resources" was published in ESMO-Open (2). On November 16th, 2020, during the 4th International Oncology Leadership Conference by the Mandrier Group, a virtual meeting was organized, involving key faculty members. They discussed new frontiers for achieving fair breast cancer care in a globalized world (Figure 2). In this article, we highlighted the main ideas and presented some recommendations. Recordings of the presentations can be found on the Senologic International Society website (www.sisbreast.org). Starting with a global vision, we tried finding solutions to identify the optimal quality of breast care, taking into account the local financial and organizational restrictions. Many important aspects are involved, such as quality management, multidisciplinary care, research, economics, regional differences (city versus rural context), information technology, interactions between patients and physicians, and media. The generated ideas are the result of discussions between more than 100 experts from 25 countries in five continents. The project is continuously evolving, and the goal is to arrive at an open-access publication that is available to everybody, without borders.

Global surveillance of cancer survival trends

Population-based survival for patients diagnosed with breast cancer is a key measure of the overall effectiveness of the local health system in managing the disease. This indicator summarizes the final result of the efficiency of early diagnosis, screening, investigation, and treatment as well as the availability of resources and local organization for breast cancer care. Global surveillance of breast cancer survival and improvement of the situation are possible only

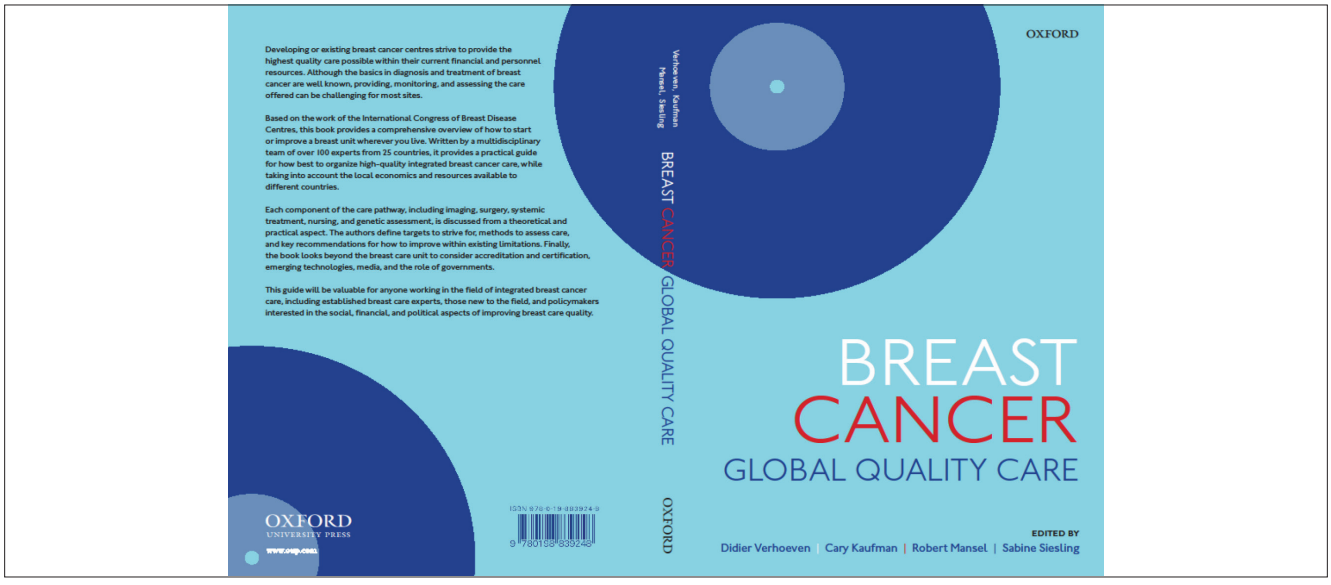

Figure 1. Breast Cancer: Global Quality Care

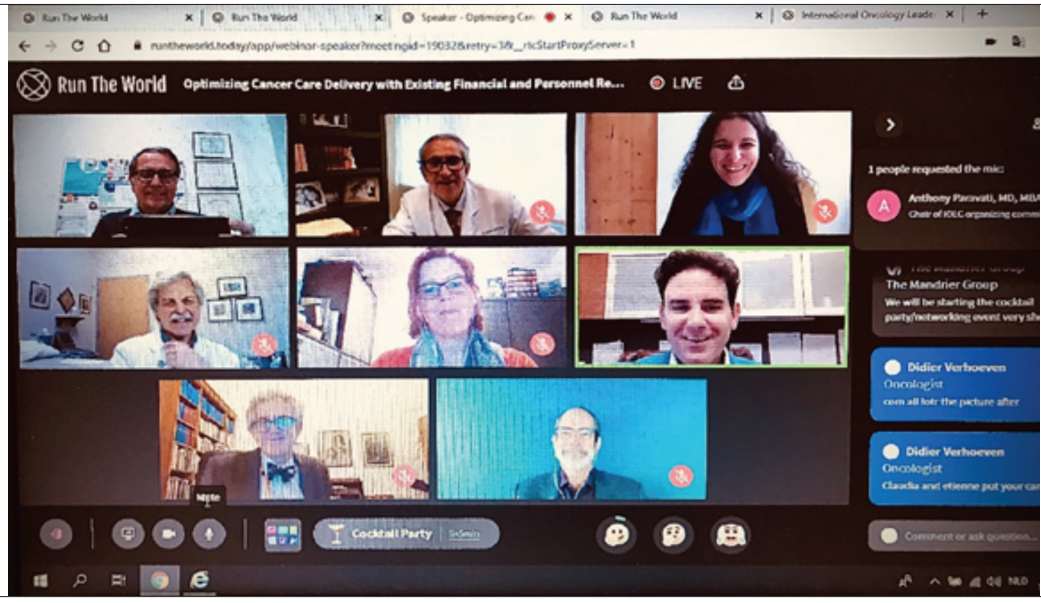

Figure 2. Participants of the virtual meeting (D. Verhoeven; M. Magalhães Costa; C. Allemani; C. Kaufman; S. Siesling; A. Paravati; E. Brain; B. Anderson; missing: M. Joore)

if we focus on monitoring the trends (the late Dr. Tabaré Vazquez, Oncologist and President of Uruguay, World Cancer Leaders' Summit, 2010). Clinical trials measure the highest achievable survival for a selected group of patients, whereas public health data measure the average survival achieved by all patients with cancer. Raising awareness regarding persistent inequalities in accessing lifesaving breast cancer services can help reduce inequalities in survival. Global surveillance of breast cancer survival trends helps identify these disparities, which can impact policies and encourage actions to reduce them (3). The third cycle of the CONCORD program for global surveillance of cancer survival provided up-to-date survival trends for 71 countries and territories, using data from 322 population-based cancer registries that cover a total population of nearly one billion people (4). For example, age-standardized five-year net-survival trends for breast cancer showed that even though survival has been increasing in all European countries over the 20-year period of 1995–2014, variability remains wide. Survival remains lower in Eastern Europe (Figure 3). These results have had an important impact on policies in different areas of the world. They impacted the following: national plans in England, France, and Poland; cancer control strategy in the European Union; survival data by state, race, and stage in the United States of America (USA) (5). Since 2017, survival estimates from CONCORD have also been officially recognized by the Organization of Economic Cooperation and Development (OECD) as one of the healthcare quality indicators for the 48 member or partner countries of OECD, and they are published in its Health at a Glance publication, www.oecd.org (6). These results also raise questions for further research. Worldwide surveillance of cancer survival trends is crucial to plan strategies for cancer control. Up-to-date data from cancer registries are essential to monitor worldwide cancer survival trends. Cancer registries need a political, legislative, and financial stable support to continue their key activities.

Multidisciplinary Breast Conference (MBC): live versus virtual

As knowledge and options have expanded in every discipline, multidisciplinary discussions have become mandatory in many countries due to their vital role in optimal patient management. The multidisciplinary breast conference (MBC) is the hub for the central exchange of knowledge at the individual patient and organizational levels to define regionally sensitive patient management. The simple criteria for a successful MBC include participants meeting regularly (usually weekly), attendance of all specialties, and integration of mutually-agreed-upon care guidelines or protocols (7) (Figure 4). MBC will frequently identify beneficial changes in management. Nevertheless, some obstacles have been identified. Time and location are inconvenient for some practices, and many cases are "not applicable to [my] specialty." In addition, many "routine" patients pose no challenge for providers, some patients need a re-discussion because of incomplete workups, and radiology and pathology specialists may complain of too much preparatory work.

To remove some of these barriers, MBC could be allowed to provide credits for continuing medical education, the most challenging cases could be discussed first, and improvements to the efficiency of patient flows must be organized. Moreover, the meetings should be supported by up-to-date technology, such as the availability of data (e.g., images) within the electronic health record and video conferences for consultants from a reference hospital. A simultaneous breakfast or lunch can be helpful in teambuilding.

The coronavirus disease-2019 (COVID-19) pandemic has brought both positive and negative changes to live meetings. Almost all MBCs are now virtual video meetings. This has caused the loss of personal interaction between clinicians, and MBC has become a more formal "business" conference. Using team meeting software programs has introduced many uncomfortable pauses, and choppy

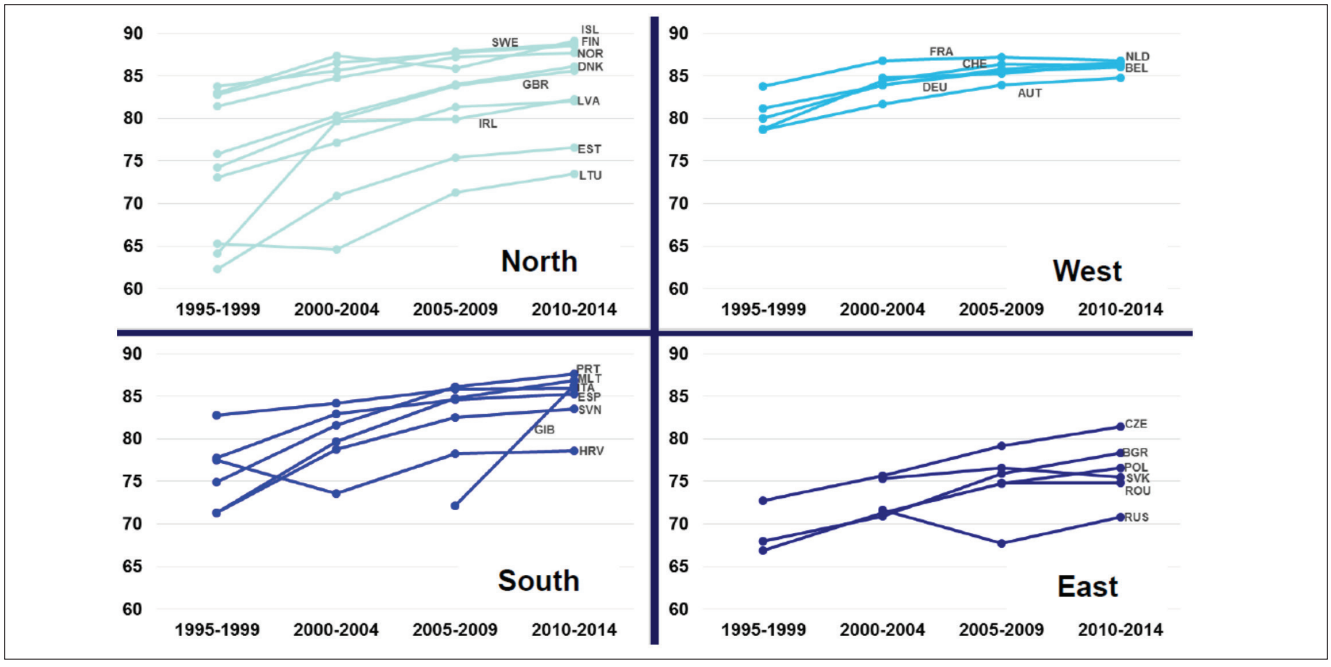

Figure 3. Breast cancer: age-standardized five-year net-survival (%) trends in European countries, 1995–2014. [Allemani et al. 2018 (4)]

FRA: France; SWE: Sweden; GBR: Great Britain/United Kingdom; IRL: Ireland; ISL: Iceland; FIN: Finland; NOR: Norway; DNK: Denmark; LVA: Latvia; EST: Estonia; LTU: Lithuania; NDL: Netherlands; AUT: Austria; CHE: Switzerland; DEU: Germany; GIB: Gibraltar; PRT: Portugal; ESP: Spain; ITA: Italy; SVN: Slovenia; HRV: Croatia; POL: Poland; BGR: Bulgaria; RUS: Russia; SNK: Japan; ROU: Romania

flow of discussion may occur due to "share screen" switching (Figure 5).

Nevertheless, some benefits are recognized. The meetings are easier to attend by saving travel time and improving access to patients' clinical data. The discussion can be held in COVID-safe environments with a more focused discussion and without distractions or side discussions.

Whether in-person or virtual, MBC remains the springboard for research and integrated treatment plans and the forum for second opinions and optimizing the management of patients with breast cancer. Although MBC will survive COVID-19, we are looking forward to meeting again in a live environment.

Value-based healthcare: myth or reality?

The value-based healthcare concept started with the book of Michael Porter and Elizabeth Taisberg: "Redefining Healthcare: Creating Value-Based Competition on Results" in 2006 (8). Value-based healthcare can be defined as the equation that puts patient-relevant outcomes in the numerator and cost per patient to achieve these outcomes in the denominator (Figure 6). Breast cancer care is costly, due to the rising incidence, increasing survival, and prevalence, with better treatment options. A complex disease such as breast cancer makes this vision even more relevant.

There is no such thing as "THE breast cancer patient." Frequently important variations in provided treatment are observed without proven benefit. An interesting example is the use of neoadjuvant chemotherapy in patients with breast cancer in Dutch hospitals. A large variation is observed, which is not related to the outcome or caseload volume of the hospital (9). Patients should be informed about their options and estimated harms and benefits and then decide, together with their treating physicians, which treatment is best according to their personal situation. The clinical and social factors should be considered. Moreover, all patient-relevant outcomes must be considered: survival and disease control reported by the cancer registries, perceived utility of care, and degree of health and distress, which can be reported by the patient-reported outcomes measures (PROMs) (https://www.ichom.org/portfolio/breast-cancer/) (10). An illustrative example is the increasing role of oncoplastic surgery for the "aesthetic breast cancer cure." With the current expectation of better survival, more attention has been turned to the cosmetic results of surgery and the opportunities to educate breast surgeons about these techniques (11). Nevertheless, although PROMs are becoming more important, making them feasible and useful in daily practice measurements must be done using a limited number of questions with direct feedback in the consultation room. Although some steps have been taken to make this a reality, in the future, more effort will be

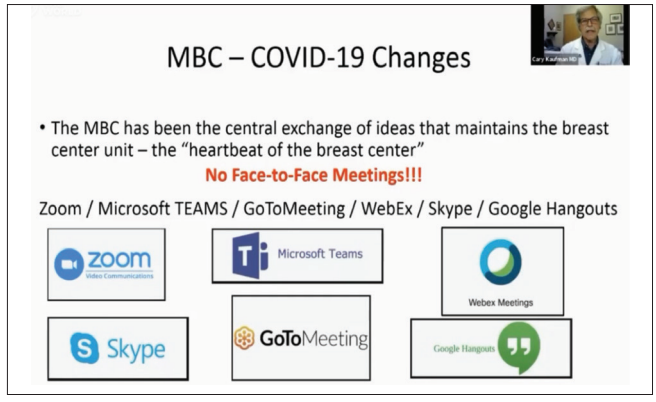

Figure 5. MBC in the times of COVID-19

MBC: Multidisciplinary Breast Conference; COVID-19: Coronavirus disease-2019

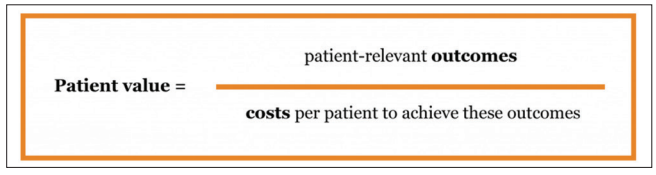

Figure 6. Definition of value-based healthcare

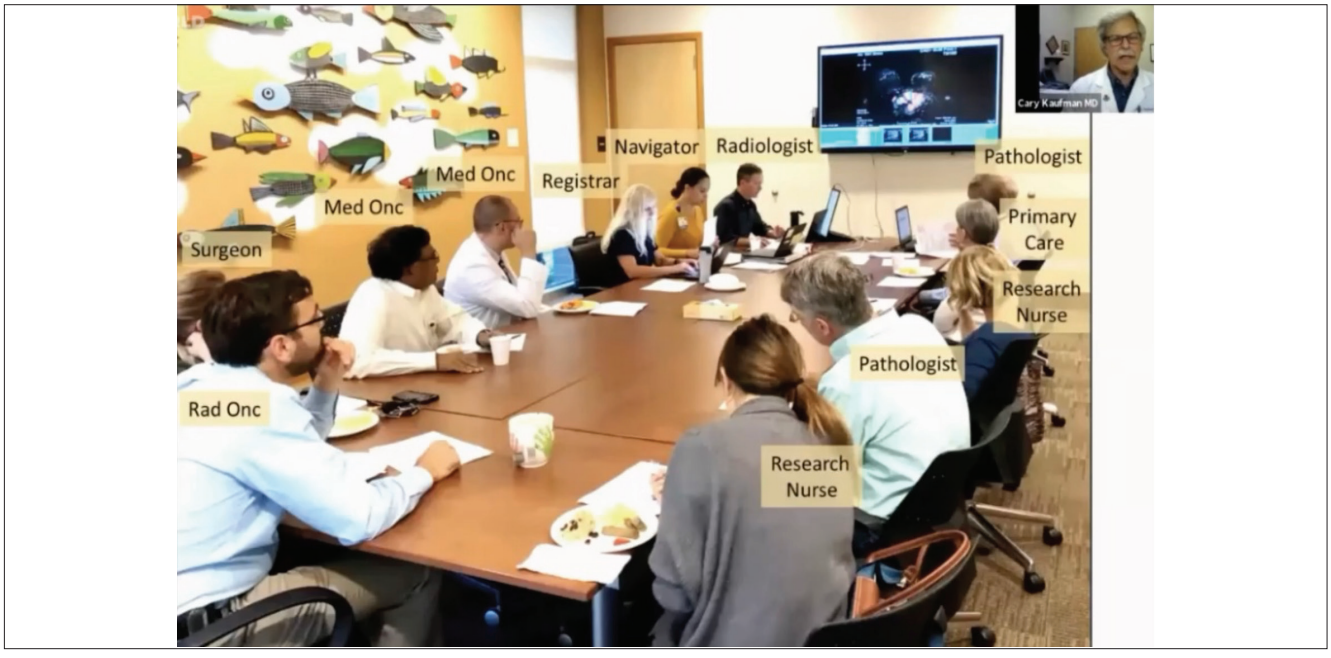

Figure 4. Interaction in MBC with participation of all disciplines at the Bellingham Regional Breast Center, Seattle, US

MBC: Multidisciplinary Breast Conference; US: United States

required to bring value to all patients in every country. The integration of healthcare quality improvement measures for health literacy, language access, and cultural access must be recommended (12).

Maximizing patient value, considering the local resources

Social healthcare expenditures, of which a considerable part is due to breast cancer care, are rising to levels that may not be sustainable in the future (13). Treatment costs of cancer are equally high both within and outside the healthcare system (14). Although these aspects are essential, the rising cost of cancer drugs is an important aspect in Europe (Figure 7). Economic evaluations of new and existing therapies can be used to inform budget allocations in a way that maximizes health outcomes and broaden the values to the patient. It is increasingly recognized that personalized care can offer more value for patients and at the same time provide value for money. It is timely that current clinical practice guidelines are revisited toward a more personalized approach, acknowledging the patient's voice and the burden of cost on society.

In low- and middle-income countries (LMIC) in Southeast Asia, approximately three of four new patients with breast cancer experience a financial catastrophe or die within one year after diagnosis. An advanced stage at diagnosis and lower socioeconomic status are significant determinants of this poor outcome. There is an urgent need for more resources to aid early detection and policies provided adequate financial protection from the treatment costs of cancer (15).

In an increasing number of jurisdictions, a threshold for an additional unit of health gain, expressed in a quality-adjusted life year, is used to determine whether a therapy provides value for money. In Figure 8, the threshold shows how effectiveness and costs of new interventions can be evaluated (16).

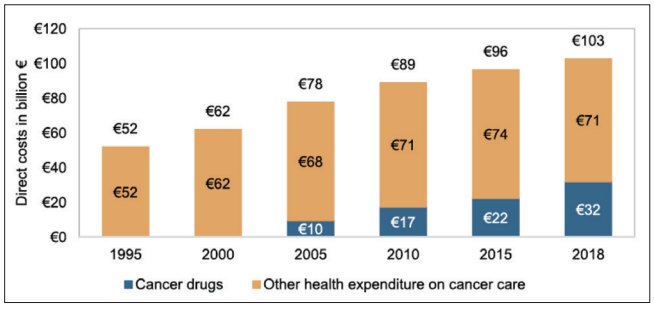

Figure 7. Direct costs of cancer in Europe (in billion) (14)

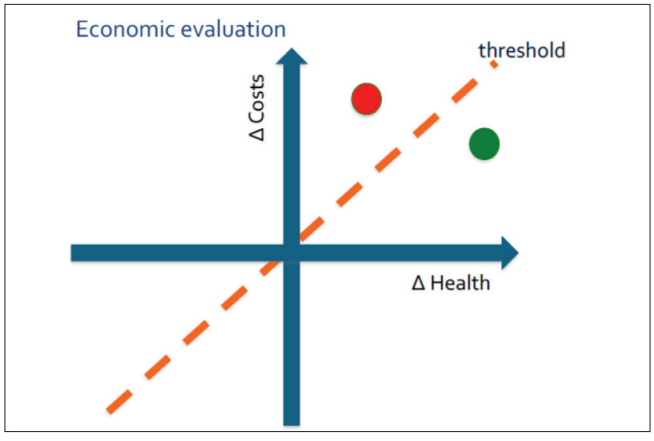

Figure 8. Cost in relation to health. The red and green dots show the economic evaluation of new interventions in relation to the acceptability threshold (16)

Improving the access to medicines by reducing the cost of cancer medications should involve trade agreements and flexibility of the Trade-Related Intellectual Property Rights (TRIPS). International patent law changes could mitigate cancer inequity in LMIC (17). The Doha Declaration affirmed the rights of states to implement policies to enable access to medicines to address the national health crisis and compulsory-license a patent for the production of generic drugs (18).

Innovations such as precision medicine may help reduce unneeded treatments, but they are associated with considerable initial costs and increasingly uncertain patient outcomes due to lack of clinical evidence. The costs hamper access: drugs do not cure anyone if patients cannot afford them. The uncertain outcomes pose a real risk to healthcare provision. The only viable road is to agree upon a broad value framework, encompassing both patient and social values. Such a framework is essential to guide a transparent, fair, and evidence-based decision making on a macrolevel. Setting a value-based price threshold can guide the allocation of our limited resources to achieve high-quality care. It can also be used to manage risks because of the uncertainty due to the lack of clinical evidence by engaging in managed entry agreements with pharmaceutical companies. This framework can also be used to support shared decision making. It integrates patient-reported outcomes, clinical evidence, and broader social considerations. It can be used to optimize personalized treatment strategies, considering the local resources.

Bringing innovations to all patients with breast cancer

Innovations and especially personalized medicine are not limited to drugs and are even sometimes more important but less popular in surgery and radiotherapy. Understanding the risk factors and causes of breast cancer must be promoted. An interesting initiative is the Sister Study in the USA prospectively examining environmental and familial risk factors for breast cancer in a cohort of 50,884 sisters of women who had breast cancer. A recent analysis suggested that, for example, substituting poultry for red meat could reduce cancer risk (19). The right design and endpoints are critical to making major advances in breast cancer care. These endpoints cannot include only the overall survival, progression-free survival, or response rate but it should also include health-related quality of life and PROMs, putting patients' values at the center of the research. Noninferiority compared with superiority, way of randomization, and relevance in the real world are critical considerations.

Clinical trials are mostly performed in younger patients, with less comorbidities and less organ dysfunction (20) (Figure 9). The recurrent discrepancy between data from trials and real world obtained from population-based cancer registries is important. The overall public health benefit must be addressed also with studies based on cancer registries, with no exclusive or partisan position. Moreover, the real-world data cannot wholly replace randomized clinical trials and require cautious interpretations to address the usual confounding factors and lack of control. In oncology, especially, the effects of the strategy of interest are often moderate or minor. In a time of a molecular tsunami with more than 100 oncogenic mutations, finding relevant ones is

challenging. So, the design of the studies must be sound, including umbrella and basket trials (21).

In the future, important strides will come from de-escalation of treatment intensity, the neoadjuvant model (as a development accelerator), addressing better and more adequately the underserved patient populations and expectations of patients with cancer themselves (22).

Many challenges can hamper the availability of innovations.

The regulation should ensure that cancer innovation enters the market not on the promise of potential benefit but on actual demonstrated effectiveness. Post-marketing studies are helpful in preventing the endless inappropriate use of new treatments.

Innovation must be balanced considering the sustainability of healthcare budgets, and all health professionals have a responsibility to help achieve this balance. Independency and academism with international sharing can help deliver innovations and bring the best outcomes possible for patients within the limits of available and limited healthcare resources.

Moving forward in a globalized world

The Breast Health Global Initiative (BHGI) was founded to bring breast cancer care as a public health priority for all women worldwide, establishing resource-stratified guidelines (www.bhgi.info) (23). Recently, methodologies were described to implement this health priority into practice (24). One of the most important challenges is the early detection of breast cancer. Understanding the differences between screening and early diagnosis is key (www.who.int) (Figure 10).

Mammographic screening is unaffordable in most countries and does not apply to younger age groups. Pragmatically, in LMIC, early

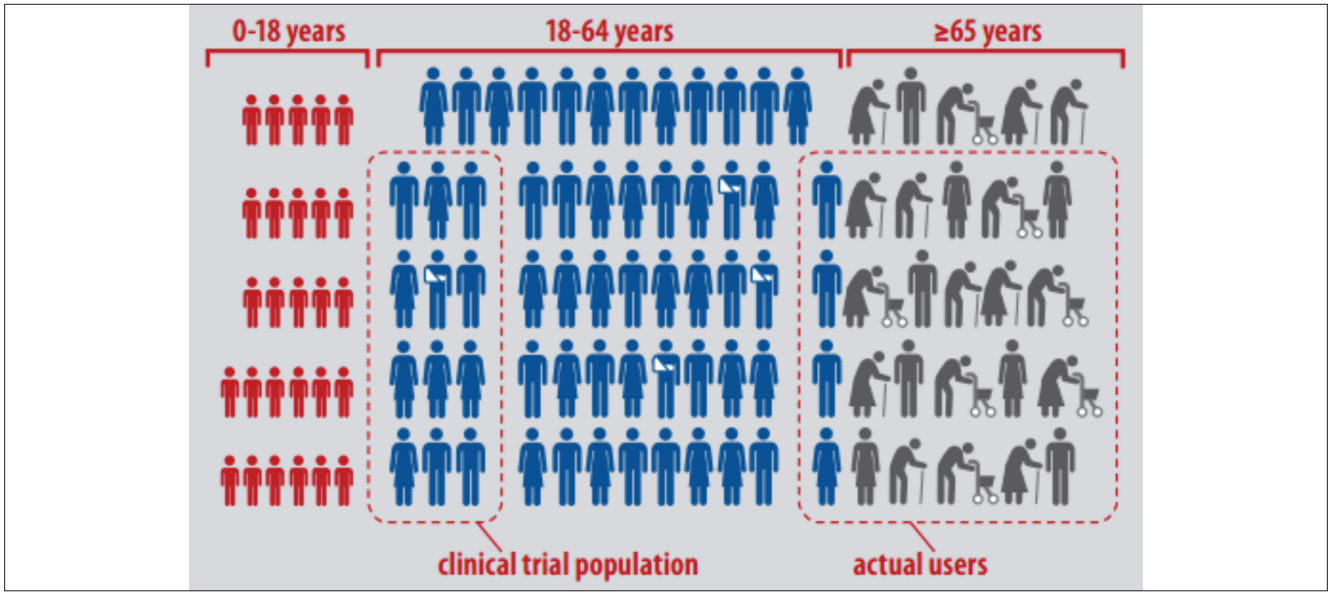

Figure 9. Trial population compared with real-life data. Actual users compared with the clinical trial population (Erna Beers, with permission, 20)

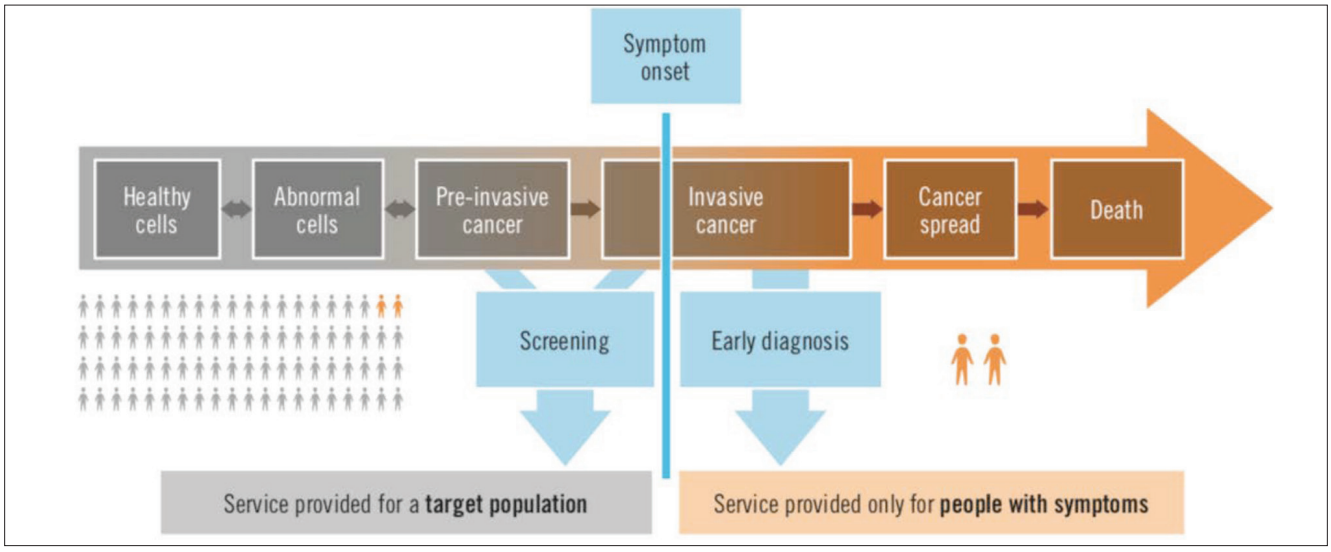

Figure 10. Understanding the difference between screening and early diagnosis (World Health Organization, reproduced from the Guide to Cancer Early Diagnosis, 2017)

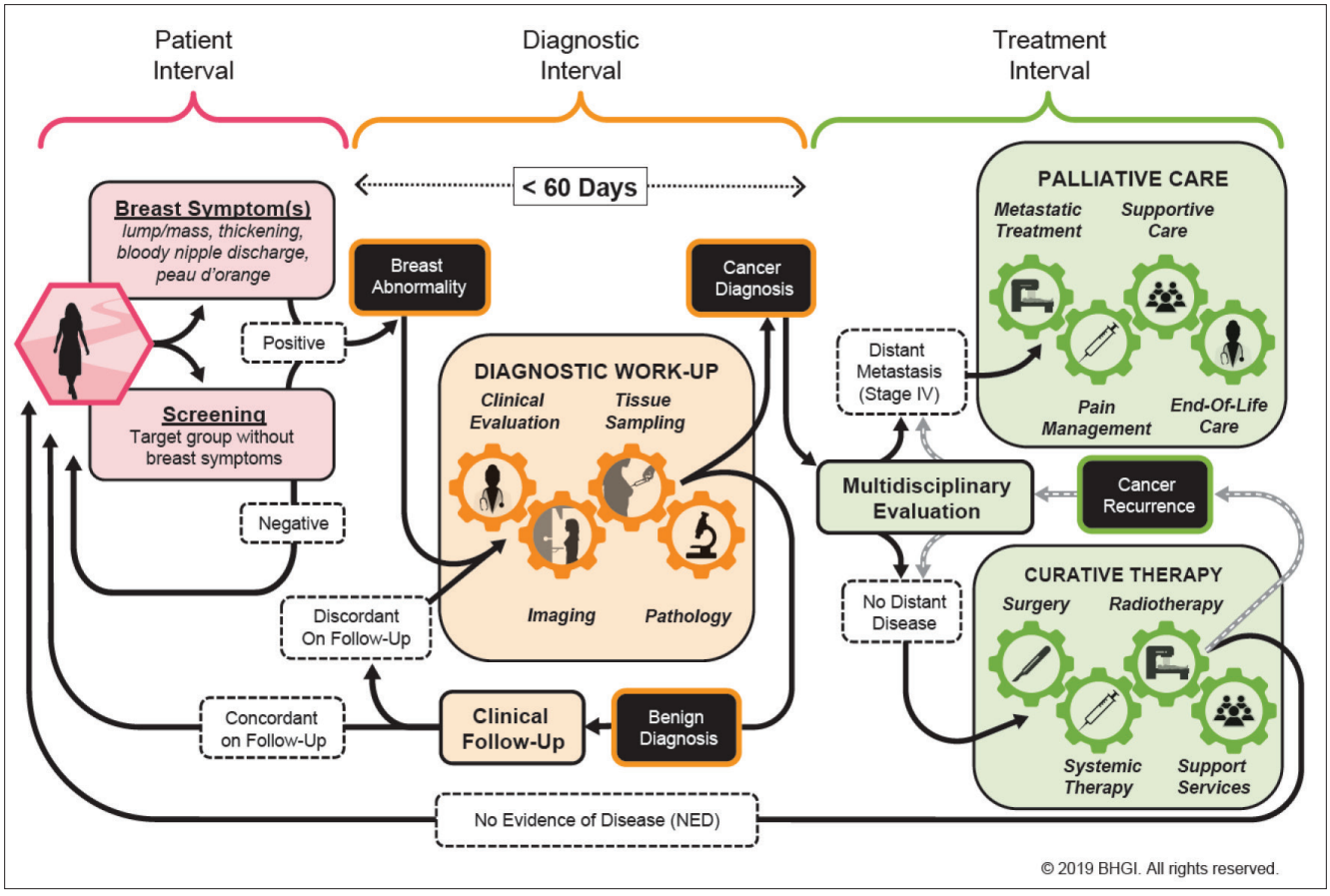

Figure 11. The three sequential episodes of breast cancer management (21)

detection involving breast awareness and clinical breast examination, linked to an integrated treatment strategy, must be organized (25). Moreover, in HIC, the harm-benefit balance must be considered and the fact that increasingly efficient therapies affect this balance. What is important is finding a screening technology that reduces the incidence rates of advanced-stage breast cancers and interval cancer rates as suggested by Philippe Autier during the "San Antonio Breast Cancer Conference 2020" (26).

The annual breast cancer mortality is currently projected to an increase of 33% by 2040. If we can reduce breast cancer mortality by 2.5%, more than 2.5 million lives will be saved by 2040. To achieve this, a global and integrated breast cancer management is proposed by the BHGI (Figure 11).

Neoliberal practices have given people some freedom in choosing their own doctors, shorter waiting times, and better facilities. It is comprised of three principles: individualism, free market, and decentralization. However, the privatization of the healthcare left 15% of Americans without healthcare, creating inequality in the quality of care between rich and poor. A proper partnership between the public and private sector with the participation of the government in healthcare must be advocated in most countries (27). Accountability mechanisms are needed for all bodies: public, private, national and international (28).

Conclusion

Recommendations for Better Breast Cancer Care (Video 2)

Video Link 2: https://www.youtube.com/watch?v=9-8klLNTeLE

Cancer registries provide insight into the burden and management of cancer. They are essential to monitor the effectiveness of health system in managing the disease and advise the authorities regarding taking appropriate measures.

Breast cancer care requires integrated teams meeting regularly and having a clinical leader within a breast unit. Multidisciplinary meetings represent a central component of breast care. Tele-oncology can be helpful, but it requires efficient preparation and technological support.

Although prevention is key with a focus on reduction in alcohol and increasing physical activities, early diagnosis remains the most important, and awareness in LMIC and screening in high-income countries (HIC) are even more important.

Quality management must be integrated into daily practice with guideline discussions and monitoring of quality indicators to control the adherence. Identification of minimal and essential requirements can help optimize care delivery with the help of existing financial and personnel resources.

Bringing value-based healthcare to patients can be obtained by putting the patient in the center. The patients should be provided with the best possible treatment ensuring that the perspective of value is captured. All

players in the field, including policymakers, providers, pharmaceutical industry, information technology providers, and payers, must try optimizing the decision making ensuring the highest value is brought to the patients. Innovations must be rewarded appropriately to the real added value. The the International Consortium for Health Outcomes Measurements initiative puts forward how value-based healthcare can be provided to breast cancer patients.

Continuous education must be provided, and the shortage of workforce, especially the primary care specialists and nurses, should be addressed. In LMIC much effort must be put trying to motivate highly educated care providers staying in their own country.

Accessibility and health coverage must be obtained for all patients. The minimally required essential cancer medicines published by the World Health Organization can help governments in making difficult decisions about the availability of essential breast cancer drugs.

Some recommendations may conserve resources, such as defining and avoiding overtreatment and overdiagnosis, reducing inefficiencies and simplify the treatments, and personalizing the follow-up based on risk of recurrence. Encouraging early diagnosis will increase the chances of survival, and the overall cost will be lower. Promoting evidence-based medicine with the personalization of the treatment, organizing breast care in networks with well-organized breast units guided by locally appropriate guidelines, encouraging widespread use of ambulatory care, and organizing quality management with a reduction in the administrative burden are recommended.

In LMIC, discussing a cancer plan is especially important. In addition, healthcare networks and health coverage must protect patients against a financial catastrophe. Social health insurance programs are important in LMIC and HIC.

In the future, a new research model must be followed with strong collaboration between academia, pharmaceutical industry, nonacademic centers, and patient coalitions, considering the practical clinical benefit of new treatments.

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Original Article

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Breast Cancer Perception Scale: Psychometric Development Study

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ABSTRACT

Objective: The Breast Cancer Perception Scale was developed using a well-supported theory, thought to be associated with breast cancer prevention behaviors. The aim of this study is to develop the Breast Cancer Perception Scale based on the Health Belief Model and conduct psychometric analysis.

Materials and Methods: The study was conducted with women aged 20 or above with a methodological design. The scale study was conducted with 572 women who were not diagnosed with breast cancer and willing to participate in the study.

Results: The results of the exploratory factor analysis revealed that the scale is made up of six sub-dimensions (perceived knowledge, perceived treatment belief, the perceived need for a health check, perceived stigma, perceived fear, perceived risk) and 24 items, which explain the 74.36% of the total variance. The model obtained from the confirmatory factor analysis was within the limits of the acceptable fit index and factor loads between 0.655 and 0.998. Cronbach's alpha reliability coefficient of the scale sub-dimensions was determined as 0.815–0.950.

Conclusion: The overall psychometric evaluation results of the Breast Cancer Perception Scale found it to be a valid and reliable instrument that can be associated with multi-dimensional cases, such as healthy life behaviors in women, breast cancer diagnostic behaviors, family history, traumatic experiences regarding breast cancer, and the level of breast cancer knowledge.

Keywords: Breast cancer, perception, reliability, validity

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Key Points

- Using a well-supported theory in the study, the Breast Cancer Perception Scale was developed, which is thought to be associated with breast cancer prevention behaviors. This scale can be used to evaluate and understand the relationship between breast cancer and breast cancer diagnostic behaviors, such as breast self-examination, clinical breast examination, getting mammography, and maintaining healthful behaviors like diet, exercise, and healthy eating.

Introduction

Breast cancer is the most common cancer type with the highest mortality rate in women globally and in Turkey (1). With early diagnosis, survival and treatment increases by 90% in breast cancers (2). For cancers with genetic and environmental risk factors, measures that focus on changeable risk factors and early diagnosis are essential strategies (3, 4). Healthy People 2020 program by the United States Office of Disease Prevention and Health Promotion objectives include reducing breast cancer mortality rate, decreasing the number of people with late-stage cancer, and improving women's breast cancer diagnosis behaviors (5). It is important for these objectives to determine women's breast cancer perceptions as breast cancer perceptions and diagnosis behaviors with healthy living are considered to be significantly associated.

Perceived breast cancer

Perception is the process of evaluating her recent experiences and past experiences and reaching a new whole (6). Understanding how breast cancer perceptions affect healthy living and early diagnosis behaviors are important to increase such behaviors. This study developed Breast Cancer Perception Scale by taking The Health Belief Model as a reference.

In the literature, women's beliefs about mammography and breast self-examination (7), their perceived sensitivity to breast cancer, and their perceived benefits and barriers to mammography use (8), fear of breast cancer (9), fatalism toward cancer (10), and their attitude toward cancer have

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scales that evaluate them separately (11). With the developed Breast Cancer Perception Scale, women's perceptions of the factors affecting breast cancer diagnosis behavior are evaluated as a whole. This scale is complementary. In addition, the perceived knowledge sub-dimension of the Breast Cancer Perception Scale has not been measured before, according to the authors' knowledge, and it is a unique scale that measures a person's breast cancer knowledge perception. The Health Belief Model is commonly used to explain breast cancer diagnosis behaviors (11-14). Therefore, this scale development study was based on the Health Belief Model. The Health Belief Model was developed by Becker and his colleagues (1974) to understand protective behaviors regarding health. It argues that people's healthcare behaviors can be affected by beliefs, values, and attitudes. According to the Model, if the beliefs and attitudes seen as problems are identified, healthcare training or offered treatment can be customized as more effective for that person (7, 8, 15). Women's breast cancer perceptions may affect their breast cancer diagnosis behavior. For this reason, it is essential to measure women's breast cancer perceptions multidimensionally. The aim of this study is to develop a Breast Cancer Perception Scale with reference to the Health Belief Model and evaluate it psychometrically.

Materials and Methods

This study is a methodological study conducted with women aged 20 and over in a district in the south of Turkey without a breast cancer diagnosis. For a psychometric analysis in a development study using a scale, it is recommended that the sample be between 10 and 20 times the number of items on the scale (16, 17). Considering the number of items, the study was completed with 572 women. The study inclusion criteria were literate, women over the age of 20, no cancer diagnosis, no communication impairment (hearing and speech), no disability to answer questions physically, cognitively, or mentally, and agreed to participate in the study. Study data were collected by the face-to-face interview method between September 2019 and March 2020. The questionnaires took approximately 10–15 minutes to answer.

Data collection forms

Descriptive characteristics form

The form consists of questions prepared by the researchers involving information on the age, education, marital status, employment status, income level, and socio-demographic characteristics. The form also includes questions regarding family history of breast cancer, regular breast self-examination, routine clinical breast examination, and routine mammography for women above 40.

Breast cancer perception scale

First, a comprehensive literature review was conducted to develop the Breast Cancer Perception Scale. The draft scale, which was initially developed with 35 items, has a 5-point Likert-type structure with responses varying between "Strongly Agree" (5) and "Strongly Disagree" (1). Some scales available in the literature were used as references to ensure the scale items' construct and criteria validity. These scales measure beliefs on breast mammography and breast self-examination (7), perceived sensitivity regarding breast cancer and perceived benefits and obstacles to mammography (8), fear of breast cancer (9), fatalism regarding cancer (10), and attitudes toward cancer (11). The formulated items were reviewed by 10 breast cancer experts. The experts reviewed all factors relevant to conceptual perception regarding breast cancer and suggested some editorial changes. Finally, 11 items were omitted based on item analyses and factor analyses and resulted in the 24-item version. The sub-dimensions of the scale are explained below.

Perceived knowledge

Perceived knowledge includes prejudices such as hidden self-confidence and unrealistic optimism (18). The perceived knowledge sub-dimension is not related to a person's knowledge level on breast cancer. It is related to how knowledgeable a person sees herself. It arouses curiosity on how a person's high perceived knowledge on breast cancer influences preventive breast cancer behaviors.

Perceived treatment belief

Perceived treatment belief can be influenced by women's spiritual and religious beliefs, previous breast cancer treatment experiences, and family breast cancer treatment stories. The studies on spirituality and health screening behavior present inconsistent findings (19-21). In this regard, a person's perceived treatment belief can affect her protective behaviors.

Perceived need for health check

Having a low perceived need for a health check is one of the primary obstacles in breast cancer screening practices among women. Women do not feel the need to go to a doctor unless they know disease signs and symptoms (22, 23). Studies showed that women in developing countries are inclined to reject the concept of early diagnosis saves lives because of their beliefs regarding having breast cancer. This has a negative effect on taking preventive measures regarding cancer (23-26). Low or high scores on the perceived need for health check may influence breast cancer protective behaviors.

Perceived stigma

The breast has a symbolic meaning that differs from other organs, as it is associated with giving birth, raising a child, and sexuality (27). This symbolic meaning can become an obstacle for women in the care, treatment, or screenings related to their breasts (27, 28). Silence regarding breast cancer and screening behaviors can be associated with the taboo perceptions about breasts (29).

Perceived fear

The level of perceived fear can impact women's breast cancer protective behavior. Studies point out that women experience fear of receiving a breast cancer diagnosis and losing one or both breasts (5, 30-32). Similarly, another study revealed that women with high breast cancer fear get fewer mammographies in 12 months (33).

Perceived risk

Perceived risk is an important factor affecting breast cancer protective behavior (5, 30-32). Witnessing their loved ones difficulties and pain during the breast cancer process increases perceived breast cancer fear and perceived breast cancer risk (34, 35). In their study, Whitney et al. (36) reported that women with high perceived risk also have a higher perceived risk for breast cancer.

Psychometric tests used

Validity

Exploratory (EFA) and confirmatory factor analysis (CFA) methods were used to determine the scale's construct validity. Before EFA, Bartlett's Test for Sphericity and Keiser-Mayer-Olkin (KMO) tests were implemented to examine the scale's content and sample size adequacy. For the sample size to be adequate for factor analysis, KMO has to

be above 0.60, and Bartlett's test for Sphericity has to be statistically significant (16, 17). Moreover, for construct validity, EFA and Direct Oblimin analysis was implemented to associated group items in a particular set (16). Following EFA, CFA was implemented to support the findings of the scale. The Goodness of Fit Indices of the model were analyzed after CFA; x^2/standard deviation (SD) rate ≤5; root mean square error of approximation (RMSEA) ≤0.08; and Goodness of Fit Index (GFI), Comparative Fit Index (CFI), and Incremental Fit Index (IFI) values of above 0.90 indicates that the model is within acceptable goodness of fit limits (16, 17, 37, 38).

Reliability

The sub-dimension item-total score correlation coefficients and Cronbach's alpha values as the internal consistency analysis for the items in the scale were calculated to determine the reliability of the adapted scale. The time invariance of the scale was assessed through the test-re-test technique applied three weeks after the first implementation with 30 participants. Pearson Product-Moment Correlation Coefficient was implemented for the test-re-test method.

Statistical analysis

The data collected from the study were analyzed through Statistical Package for the Social Sciences (SPSS) 23.0 for Windows software (SPSS Inc, Chicago, Illinois) and Analysis of Moment Structures (AMOS) 24.0. Descriptive statistics such as percentage, frequency, minimum-maximum values, mean, and standard deviation were used to analyze socio-demographic data. EFA and CFA techniques were implemented for the construct validity of the scale. The direct Oblimin method was used in the EFA. Bartlett's test for Sphericity and KMO tests were implemented for the scale content and sample size adequacy. CFA was used to examine the factor construct and factor loads of the scale. A t-test and Pearson product-moment correlation tests were implemented to determine the relationship between the repeat measurements. The significance level was accepted as 0.05.

Ethical approval

The ethical considerations of the study were evaluated by the Akdeniz University Clinical Studies Ethics Board, and ethical approval was received (number of meetings: 78; decision number: 727; date of decision: 24.07.2019). Patients in the sample were informed about the study, and their written consent was also received for the study.

Results

Descriptive characteristics of patients

In the study involving 572 women; It was found that the mean age of the women who participated in the study was 45.79±14.85, 33.7% was aged 20–29, 28.1% was elementary school graduate, 71.2% was married, 43.2% was housewife, and 55.9% perceived their income and expense levels as equal. Of all participating women, 50.9% sometimes conducted breast self-examination, 68.0% never had clinical breast self-examination, 40.8% of the women aged above 40 never had mammography, and 84.4% were found to have a family history of breast cancer (Table 1).

Content validity

The formed scale was sent to 10 expert faculty members (three public health nursing, one internal medicine nursing, two surgical nursing, and three psychiatric nursing). Davis' technique was used for content validity. The content validity index values of the draft scale were found to be 0.93 on average and varied between 0.60 and 1.00. Upon evaluating the comments from the experts, the scale was implemented to 30 women. These 30 women participants were not included in the study. Each item was found evident in the pre-implementation stage, so no changes were deemed necessary for the scale.

Psychometric test results

Validity

Before factor analysis, the KMO sampling adequacy test and Bartlett's test for Sphericity were implemented to determine whether the sample was adequate and the factor correlation matrix was good for fit. KMO value was found as 0.770, and Bartlett's test for Sphericity result was determined as $x^2 = 9{,}231.271$ ($p = 0.000$).

First, EFA was conducted to determine the number of sub-scales. The analysis showed that the scale has a 6-factor construct with a self-value above 1.00. The direct Oblimin Method was preferred for factor analysis implementation to keep the relationship between factors stable. The variance explanation rate was 74.36%. As a result of EFA, 11 items from the 35-item breast cancer detection scale items were excluded from the scale because the factor load was less than 0.30. The scale sub-dimensions were found and named Perceived Knowledge, Perceived Treatment Belief, Perceived Need for Health Check, Perceived Stigma, Perceived Fear, and Perceived Risk. According to EFA, the scale's item factor loads vary between 0.621 and 0.952 (Table 2).

CFA was conducted to evaluate the construct validity of the Breast Cancer Perception Scale. The model was within the good fit limits as the RMSEA value was 0.072; chi-square value was statistically significant ($\chi^2 = 830.577$; n = 572, SD = 210 p = 0.00), $\chi^2/SD = 830.577/210 = 3.954$; CFI value was 0.933; GFI value was 0.913, Bentler-Bonett Normed Fit Index (NFI) value was 0.901 and RMSEA value was 0.072. The CFA results of the items in the scale showed that the factor loads varied between 0.655 and 0.998.

Reliability

The scale consists of 24 items. High scores from the sub-dimensions indicate an increased perception regarding the relevant sub-dimension. There is the total score for the scale, and items 7, 9, 10, 11, 12, and 13 are reversely coded. The item-sub-dimension total correlation coefficients resulted from the reliability analysis and varied between 0.670 and 0.956 (Table 2).

Cronbach's alpha as the internal consistency was calculated to measure the reliability of the scale. Cronbach's alpha coefficients of the scale's sub-dimensions varied between 0.815 and 0.950 (Table 3).

The difference between the scores collected from two measurements of the draft scale repeated with a 3-week interval was analyzed through a t-test with dependent groups. The difference between the two implementations of all sub-dimensions was not statistically significant. Pearson's product-moment correlation coefficient analysis showing the consistency between the test-retest score averages of the scale showed a statistically significant, positive, and strong relationship (0.946–0.994) between the two scale sub-dimension measurements (Table 4).

Discussion and Conclusion

This study presents preliminary evidence that breast cancer perception, as a construct, can be measured in a valid and reliable way. The Breast

Cancer Perception Scale, which is thought to be associated with breast cancer protective behaviors, was developed in the study using a well-supported theory. There are scales in the literature that measure the beliefs on mammography and breast self-examination (7), perceived sensitivity toward breast cancer, and perceived benefits and obstacles of using mammography (8), fear of breast cancer (9), fatalism regarding cancer (10), and attitudes toward cancer (11). Although, according to the Health Belief Model, obstacles to cancer screening have been measured before. This scale enables more subjective measurements with the perceived need for health check, perceived stigma, perceived fear, and perceived risk sub-dimensions. The item pool was created by reviewing the relevant literature (7-11). As suggested by the literature, the items of the scale were finalized following expert opinions, the pilot study, and factor analyses (16, 17).

KMO coefficient and Bartlett's test for Sphericity tests are used to assess the goodness of fit in terms of the scale's construct validity (16, 17, 39). When the KMO value is above 0.50, it shows that the factor analysis can be implemented. KMO value of above 0.60 and close to 1 indicates that the data is suitable for factor analysis; KMO value between 0.70 and 0.80 indicates average; between 0.80 and 0.90 shows good; and above 0.90 indicates perfect sample adequacy (40). In the case of Bartlett's test for Sphericity being significant, the correlation matrices of the scale items are suitable for factor analysis (16, 39). In this study, the KMO value was 0.770, and Bartlett's Test for Sphericity was significant ($p = 0.000$). These results indicate that the study's sample size is adequate for factor analysis, and factor analysis for the scale can be implemented.

Factor load values for the scale items must be minimum of 0.30, and items with a value lower than this need to be omitted from the scale (17, 37, 38). As a result of the EFA, 11 items from the 33-item Breast Cancer Perception Scale were removed. Their factor load values were below 0.30, and the remaining 24 items were categorized under five sub-dimensions. While interpreting the EFA results, it is expected to explain a minimum of 30% of the variance in single-factor scales and 50% of the variance in multi-factor scales (41). It was seen in this study that 74.360% of the variance in the scale is explained (Table 2).

Table 1. Distribution of characteristics and behaviors to diagnose breast cancer

		n	%
Age (45.79±14.85)	20–29 age	193	33.7
	30–39 age	144	25.2
	40–49 age	102	17.8
	50–59 age	82	14.4
	60–69 age	51	8.9
Education	Literate	51	8.9
	Primary school	161	28.1
	Secondary school	122	21.3
	High school	106	18.5
	University	132	23.1
Marital status	Married	407	71.2
	Single	165	28.8
Occupation	Homemaker	247	43.2
	Farmer	151	26.4
	Public official	111	19.4
	Worker	21	3.7
	Self employed	6	1.0
	Retired	36	6.3
Economic status	Income < expenditure	191	33.4
	Income = expenditure	320	55.9
	Income > expenditure	61	10.7
Breast self-examination	Never	224	39.1
	Sometimes	291	50.9
	Always regular	57	10.0
Clinical breast examination	Never	389	68.0
	Sometimes	129	22.6
	Always regular	54	9.4
Mammography (over 40 age) (n = 235)	Never	96	40.8
	Sometimes	88	37.5
	Always regular	51	21.7
Familial history of breast cancer	Yes	89	15.6
	No	483	84.4

n: Number

In the CFA implemented at the last step of validity analysis, the factor loads of the scale and scale consistency values were examined. CFA confirmed the construct of six sub-dimensions resulting from the EFA. According to the CFA, the factor loads of the items in the scale ranged between 0.655 and 0.998.

While interpreting the goodness of fit values of the model, it was found to be within the goodness of fit limits as the RMSEA value was 0.072; chi-square was statistically significant (χ^2 = 830.577; n = 572; SD = 210; p = 0.00) and (χ^2/SD = 3,043.701/934 = 3.259); CFI value was 0.933 and GFI value was 0.913 and NFI value was 0.901. The

Table 2. Item total correlation values, reliability coefficients, and exploratory factor analysis values

Item no	Items	Mean (SD)	Factor loading	% of variance	Cumulative %	r
Perceived knowledge						
1	My knowledge of breast cancer treatment is sufficient	2.81±1.11	0.902	19,353	19,353	0.909
2	I think that I have sufficient knowledge of breast cancer	2.83±1.13	0.887			0.871
3	I know what women who had breast cancer treatment should pay attention to	2.79±1.14	0.877			0.875
4	I know how to be protected from breast cancer	2.89±1.19	0.831			0.854
Perceived treatment belief						
5	It is important for early diagnosis and treatment to attend screenings regularly	3.88±1.18	-0.848	14,685	34,039	0.843
6	Early diagnosis of breast cancer increases the chances of recovery	3.84±1.14	-0.840			0.837
7	Breast cancer is a treatable disease	3.58±1.18	-0.822			0.823
8	Breast self-examination is important for early diagnosis and treatment	4.10±1.16	-0.786			0.773
9	Breast cancer treatment does not change the outcome	4.06±1.10	-0.621			0.670
Perceived need for health check						
10	I do not go to the doctor unless there is a disease finding	3.33±1.09	-0.952	13,482	47,521	0.954
11	I forget to get a regular breast examination	3.40±1.08	-0.950			0.956
12	It does not come to my mind to go to a regular breast examination	3.44±1.05	-0.914			0.901
13	I am reluctant to be examined by a male doctor	3.27±1.07	-0.902			0.920
Perceived stigma						
14	Women with breast cancer experience problems in their sexual lives	2.56±1.13	-0.869	11,740	59,260	0.850
15	Women with breast cancer cannot take care of their children	2.44±1.12	-0.839			0.831
16	Women with breast cancer experience problems in their marriages	2.68±1.17	-0.795			0.797
17	Breast cancer treatment makes a woman less beautiful	2.56±1.27	-0.688			0.738
Perceived fear						
18	It scares me to think of breast cancer	3.40±1.18	-0.909	7,794	67,054	0.892
19	I feel uncomfortable when I think of breast cancer	3.31±1.31	-0.873			0.866
20	It makes me feel uneasy to think about the breast cancer treatment process	3.21±1.25	-0.854			0.860
21	The thought of having breast cancer worries me	3.17±1.33	-0.780			0.824
Perceived risk						
22	I see myself under the risk for breast cancer	3.10±1.12	0.912	7,306	74,360	0.925
23	The risk for breast cancer is higher in those with a family history of breast cancer	3.22±1.08	0.850			0.853
24	I think that my chance of having breast cancer is high	2.98±1.15	0.848			0.850

SD: Standard deviation; r: Sub-dimension item-sub-dimension total correlation

Table 3. Scale subscale scores and Cronbach's alpha values

	Cronbach's alpha	Mean ± SD (min-max)
Perceived knowledge	0.900	2.82±1.00 (1–5)
Perceived treatment belief	0.850	3.89±0.91 (1–5)
Perceived need for health check	0.950	3.36±1.00 (1–5)
Perceived stigma	0.815	2.56±0.96 (1–5)
Perceived fear	0.896	3.27±1.09 (1–5)
Perceived risk	0.848	3.10±0.98 (1–5)

SD: Standard deviation; min: Minimum; max: Maximum

Table 4. Test-retest analysis of the scale

	Items	n	Test Mean ± SD (min-max)	Re-test Mean ± SD (min-max)	t-test p	r p
Perceived knowledge	4	30	2.66±1.09	2.53±1.19	-1.112 0.331	0.958 0.000
Perceived treatment belief	5	30	4.03±0.98	3.97±0.93	-0.795 0.432	0.946 0.000
Perceived need for health check	4	30	3.12±41.17	3.09±1.75	-0.571 0.573	0.994 0.000
Perceived stigma	4	30	2.40±0.80	2.41±0.82	0.558 0.592	0.957 0.000
Perceived fear	4	30	3.40±1.30	3.46±1.31	1.439 0.161	0.981 0.000
Perceived risk	3	30	3.04±0.981	3.01±0.963	–1.278 0.211	0.982 0.000

t-test: Paired Sample t-Test; r: Correlation between two measurements; n: Number; min: Minimum; max: Maximum; SD: Standard deviation

literature indicates that x^2/SD rate ≤5; RMSEA ≤0.08; and GFI, CFI, and IFI values above 0.90 shows that a model is within the acceptable fitness limits (16, 17, 37, 38).

As a result of the reliability analysis, it was determined that the item-sub-dimension total correlation coefficients ranged between 0.670 and 0.956 (Table 2). The lowest rate for item-total score correlation coefficient was considered as 0.20. The items with a correlation coefficient between 0.30–0.40 are reported as "good," and items above 0.40 are "very good" (17, 39).

Cronbach's alpha as the internal consistency coefficient was calculated to determine the scale's reliability value. Cronbach's alpha coefficients of the sub-dimensions varied between 0.815 and 0.950. It is reported that Cronbach's alpha coefficient may vary between 0.0–1.0; a coefficient between 0.60 and 0.80 represents a reliable scale; a value of 0.80 and above represents a highly reliable scale (16). In this regard, Cronbach's alpha values found in our study are consistent with the highly reliable values reported in the literature.

Another reliability test is the investigation of test-retest scores of the scale (16, 39). With this test, the correlation coefficients collected from two measurements taken at certain time intervals are examined and determined to what extent the test provides time consistent results. A high correlation represents the consistency of test scores and the little variance over time between the two measurements (16). The correlation coefficients between the test-retest sub-dimension scores (0.946–0.994) were very high (Table 3). These findings showed that the scale is a consistent instrument against time and has time consistency.

There are certain limitations to be considered when evaluating these study results. The study's limitations are that it was conducted in a single region, and the correlation was not conducted with similar scales.

It is important to know and measure how breast cancer is perceived by women in developing breast cancer preventive behaviors. This study, which was conducted based on The Health Belief Model, found unique characteristics regarding how breast cancer is perceived by women. This scale can be used to evaluate and understand the relationship between breast cancer and breast cancer diagnostic behaviors, such as breast self-examination, clinical breast examination, getting mammography, and maintaining healthful behaviors like diet, exercise, and healthy eating. The Breast Cancer Perception Scale is also a valid and reliable instrument to be used in relational studies on breast cancer knowledge and familial history.

Ethics Committee Approval: The ethical considerations of the study were evaluated by the Akdeniz University Clinical Studies Ethics Board, and ethical approval was received (number of meetings: 78; decision number: 727; date of decision: 24.07.2019).

Informed Consent: Patients in the sample were informed about the study, and their written consent was also received for the study.

Authorship Contributions

Concept: S.T., İ.Ö., D.A.; Design: S.T., İ.Ö., D.A.; Data Collection or Processing: S.T., İ.Ö., D.A.; Analysis or Interpretation: S.T., İ.Ö., D.A.; Literature Search: S.T., İ.Ö., D.A.; Writing: S.T., İ.Ö., D.A.

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Original Article

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Cytological Evaluation of Pathological Male Breast Lesions

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ABSTRACT

Objective: This study aimed to determine the cytodiagnostic spectrum of various male breast lesions, which were corroborated on histopathology as appropriate, to describe the process of the cytomorphology of some uncommon pathological lesions, and to discuss the reasons of their misdiagnoses.

Materials and Methods: In this 8-year study, a total of 114 patients underwent fine needle aspiration cytology (FNAC). In a representative case, nipple discharge from an 8-month-old child was examined. Confirmatory histopathology was obtained in 38 cases only.

Results: Gynecomastia was the most common (63.5%) male breast pathology. Invasive breast carcinoma of no special type was the most common variant of male breast malignancy. Half of the "gray zone" of cytological lesions was confirmed as cancer, but the rest were diagnosed as fibrocystic disease and intraductal papilloma. All cases with malignant cytology matched their corresponding histopathology. However, a tumor from an intraductal papillary carcinoma was miscued as ductal carcinoma on previous FNAC.

Conclusion: Cytological evaluation of male breast lesions provides highly sensitive and specific results with excellent histologic reproducibility. Thus, it should be the ideal pretherapeutic diagnostic procedure for male breasts. However, some benign pathological conditions, which are particularly associated with epithelial hyperplasia, perplex the cytomorphologic scenario into the "gray zone."

Keywords: Breast carcinoma, fine needle aspiration cytology, gray zone, gynecomastia, male breast

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Key Points

- Breast pathology is a relatively ignored entity in men, so they are often diagnosed late on the course.
- The most important utility of male breast cytology is to discriminate gynecomastia from any other neoplastic lesions.
- "Gray zone" cytological interpretation is the major pitfall of breast cytology, as it encompasses benign lesions as much as cancerous lesions.

Introduction

Morphologically, the male breasts, like its female counter organs, consist of glandular and adipose tissues. However, in men, glandular units are composed of ducts only, which are typically circumscribed underneath the nipple-areolar complex (1). Pathological lesions in male breasts are not common. Gynecomastia is the most common lesion in men. Its prevalence varies from 32% to 65% with respect to age groups. In postmortem male breast specimens, gynecomastia has been reported in 45%–50% of the cases (2). Similarly, carcinomas rarely occur in male breasts. It accounts for 1% of all breast cancer cases arising in both sexes, and approximately 1% of all malignancies occur in men. Clinically, it resembles gynecomastia as well as any other benign pathological lesions associated with male breast enlargement. Therefore, urgent discrimination of these two contrasting pathological entities is necessary (3). For this purpose, core needle biopsy and the recently amended vacuum-assisted breast biopsy are the most useful diagnostic method. However, as the most common male breast pathology, gynecomastia is best cured conservatively; it is therefore unreasonable to consider biopsy as the primary diagnostic intervention. On the contrary, fine needle aspiration cytology (FNAC) provides prompt and precise diagnoses economically and conveniently (4, 5). This study aimed to cytologically evaluate various pathological lesions that affect the male breasts and to validate the diagnostic accuracy of FNAC against the histopathology wherever practicable.

Materials and Methods

This study was approved by the state ethics committee and was accomplished at the Department of Pathology, Sonoscan Healthcare, Malda, India; after acquiring approval from the State Ethics Committee (Ethics Committee Pathology 2010, Sl no: 437/L) on 7th of December, 2010.

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Written informed consent was procured from each patient after explicit explanation of the procedures was provided.

From January 2011 to December 2018, a total of 115 male patients presented with breast lesions. All of them underwent FNAC, except for the 8-month-old infant who was brought for unilateral blood-tinged nipple discharge. The secretion was collected for exfoliative cytology by gentle concentric compression over the nipple. At FNAC, a 24-G disposable needle was utilized. Leishman-Giemsa and Papanicolaou stains were routinely applied for the air-dried and ethanol-fixed smears, respectively. Ziehl-Neelsen (ZN) staining was performed in selective cases. Only 38 patients underwent histopathological corroboration. Statistical analysis was performed in determining the sensitivity, specificity, and positive and negative predictive values of the aspirates.

Results

The patients were 8 months to 91 years old (43.8±19.9), and the median age was 48 years. Unilateral involvement of the right and left breasts were observed in 50 and 47 patients, respectively. Eighteen patients had bilateral pathologies. All bilateral lesions were cytologically diagnosed as gynecomastia, except in a single case of fibrocystic changes (FCC). In all patients, gynecomastia was the most common male breast pathology. It was isolated from 73 (63.5%) cytological samples. Other uncommon benign diagnoses included suppurative mastitis/abscess (N = 4, 3.5%), tuberculous mastitis (N = 4, 3.5%), lipoma (N = 3, 2.6%), benign cyst (N = 2, 1.7%), chronic nonspecific mastitis (N = 2, 1.7%), subareolar abscess (N = 2, 1.7%), fat necrosis (N = 1, 0.9%), FCC (N = 1, 0.9%), mammary duct ectasia (N = 1, 0.9%), and benign papilloma (N = 1, 0.9%). Of the above-mentioned cases, histopathological examination was performed for 16 lumps of gynecomastia, recurrent chronic inflammatory lesion, all cases of lipoma, and benign papilloma (Table 1).

Aspirates from the gynecomastia demonstrated moderate-to-high cellularity, with numerous tightly cohesive sheets of bimodal epithelial-myoepithelial cells and bipolar nuclei stripped at the background (Figure 1). Of the 73 lumps, 16 were confirmed histologically (Figure 2). The suppurative lesions expressed numerous polymorphs and some histiocytes. Epithelial cells, when present, showed regenerative changes and became barely discernible from the histiocytic clusters. Culture isolated two cases of methicillin-sensitive *Staphylococcus aureus* and one case each of methicillin-resistant *S. aureus* and *Streptococcus pyogenes*. Aspirates from the subareolar abscess were characterized by anucleated squames, foreign body-type multinucleated giant cells, neutrophils, and macrophages (Figure 3). Granulomatous syncytial aggregates of epithelioid histiocytes, isolated lymphohistiocytic cells, background caseous necrosis, and presence of acid-fast bacilli on the ZN-stained smears were diagnostic features for tuberculosis. Two of four patients simultaneously suffered from ipsilateral axillary tuberculous lymphadenitis. Calcified healed thoracic foci of old tuberculosis were identifiable in all four cases. Fat

Table 1. Cytological and histopathological distribution of all male breast lesions (n = 115)

Diagnostic categories	Cytological diagnosis/findings (Number of cases)	Cases correlated on histopathology	Histopathogical diagnosis
Cystic (total of 3 cases)	Benign cysts (2)	None	NA
	Fibrocystic disease (1)	None	NA
Inflammatory (total of 14 cases)	Suppurative mastitis/abscess (4)	None	NA
	Tuberculous mastitis (4)	None	NA
	Chronic inflammation (2)	1	Lymphocytic mastopathy
	Subareolar abscess (2)	None	NA
	Fat necrosis (1)	None	NA
	Mammary duct ectasia* (1)	None	NA
Benign neoplastic (total of 77 cases)	Gynecomastia (73)	16	Gynecomastia
	Lipoma (3)	3	Lipoma
	Benign papilloma (1)	1	Intracystic papilloma
Atypical (total 4 cases)	Proliferative breast disease with atypia (4)	4	Two cases of invasive breast carcinoma-no special type, one each of fibrocystic disease, and intraductal papilloma
Malignant (total of 12 cases)	Ductal carcinoma (10)	10	One case of intraductal papillary carcinoma, Rest (9 tumors) invasive breast carcinoma-no special type
	Metaplastic carcinoma (1)	1	Basaloid squamous cell carcinoma
	Mucinous carcinoma (1)	1	Mucinous carcinoma
Non-diagnostic (Total of 5 cases)	Adipocytes only	1	Gynecomastia

*Only case that underwent exfoliative cytological examination.
NA: Not available; n: Number

necrosis yielded fragments of mature and poly-vacuolated degenerated adipose tissue, foamy macrophages, multinucleated giant cells, and lymphocytes, with a muddy background of granular debris and lipid droplets. No epithelial component was present (Figure 4). Both lesions of chronic nonspecific mastitis yielded scanty lymphocytes and macrophages. One of the lesions was biopsied on recurrence. It featured atrophied ductules mantled immediately by lymphocytic aggregates and further surrounded by dense fibrosis. Therefore, the diagnosis was lymphocytic mastopathy (Figure 5). The patient with FCC complained about bilateral mastalgia. FNAC findings from both breasts appeared fluidy with moderate cellularity. The epithelial aggregates showed mild nuclear enlargement and ample well-defined granular cytoplasm. The background contained many cyst macrophages and some lymphocytes (Figure 6). Both mammary cysts expressed thin mucoproteinaceous fluid with multiple floating foamy macrophages. Epithelial sheets were observed rarely. The benign papilloma presented as a minute subareolar nodule. On cytological smears, the epithelial cells formed into tightly cohesive complex micropapillary clusters over a background of cyst fluid and stripped nuclei (Figure 7). On histopathology, it was diagnosed as an intracystic papilloma (Figure 8). The infant patient in this study

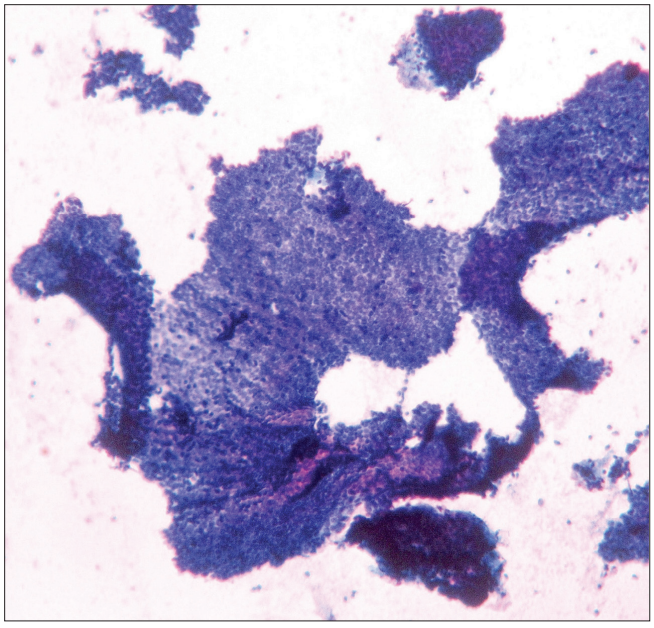

Figure 1. Cytologically, compact folded sheets of benign epithelial cells and stripped bipolar nuclei in gynecomastia (Papanicolaou staining, ×40)

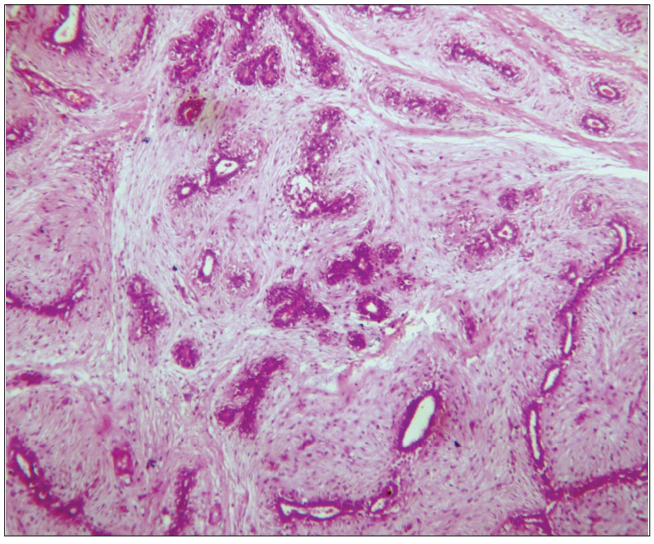

Figure 2. Representative histomorphology of gynecomastia characterized by florid epithelial hyperplasia surrounded by paucicellular fibrotic stroma (hematoxylin-eosin staining, ×40)

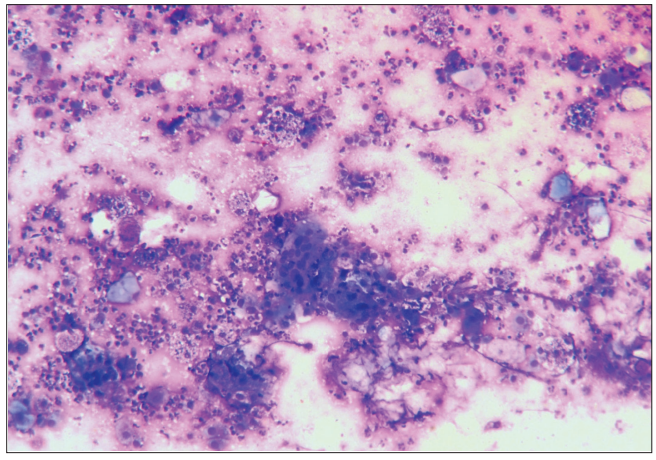

Figure 3. Subareolar abscess on cytology: scattered neutrophils, anucleated squames, and multinucleate giant cells (Leishman-Giemsa staining, ×40)

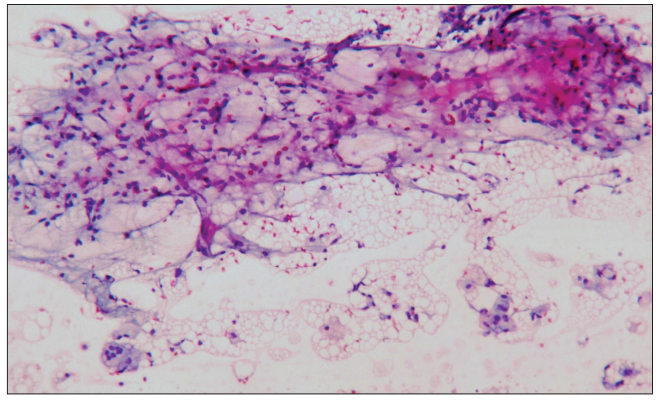

Figure 4. Cytologically, degenerating adipocytic fragments, foamy histiocytes, giant cells, and background fat vacuoles characteristics of fat necrosis (Papanicolaou staining, ×40)

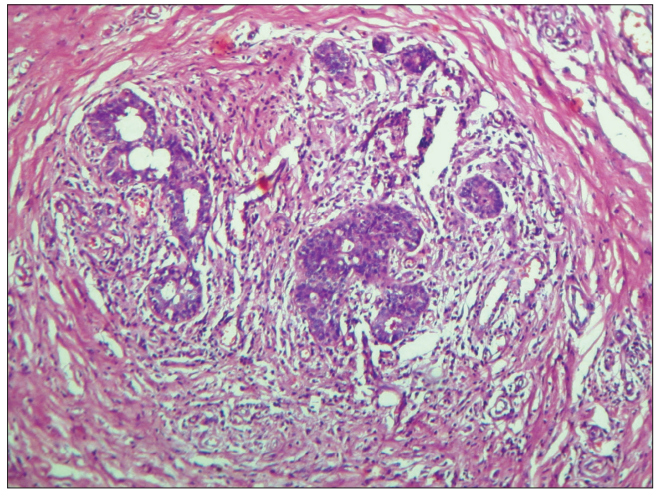

Figure 5. Histology of lymphocytic mastopathy: atrophic ductules surrounded by lymphocytic infiltrates and collagenous fibrosis (hematoxylin-eosin stain, ×40)

was brought with recurring blood-tinged discharge from his right nipple for 2 months. On palpation, any mass defect could not be identified. He had no history of trauma or familial bleeding diathesis. His endocrine activity remained within normal limits. The left breast was symptom-free as well. Nipple secretion was collected by gentle manipulation of the right areola. On microscopic examination, the exfoliative cytological smears were populated with siderophages, blood components, proteinaceous debris, and occasional epithelial cells (Figure 9). He was diagnosed with unilateral mammary duct ectasia. During follow-up, the discharge spontaneously tailed off to disappear ultimately within 4 months and did not recur on annual follow-up.

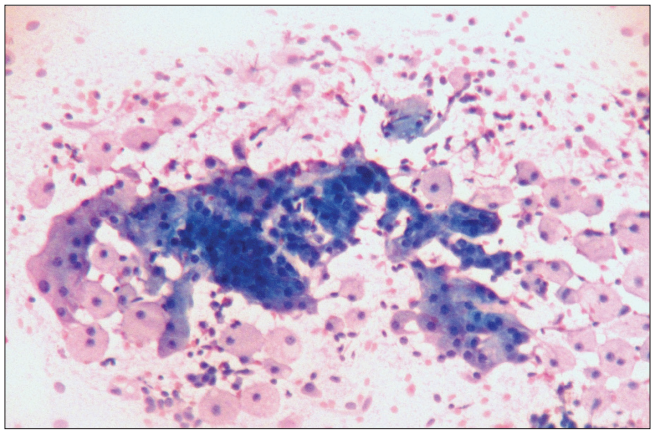

Figure 6. Cytomorphologically, apocrine epithelial changes, cyst macrophages and lymphocytes define fibrocystic changes (Papanicolaou staining, ×100)

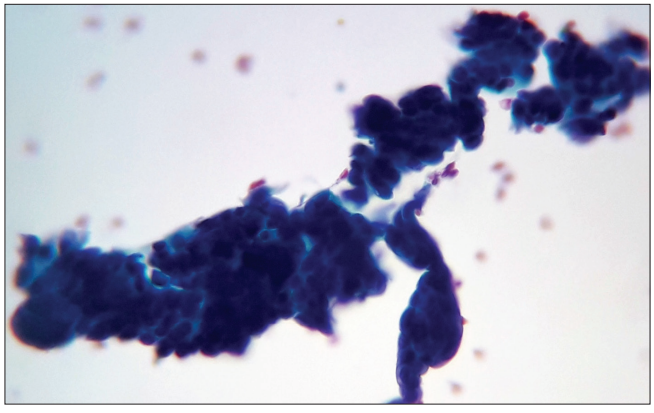

Figure 7. Compact overlapping and arborizing micropapillary fragments of epithelial cells aspirated from benign papilloma (Papanicolaou staining, ×400)

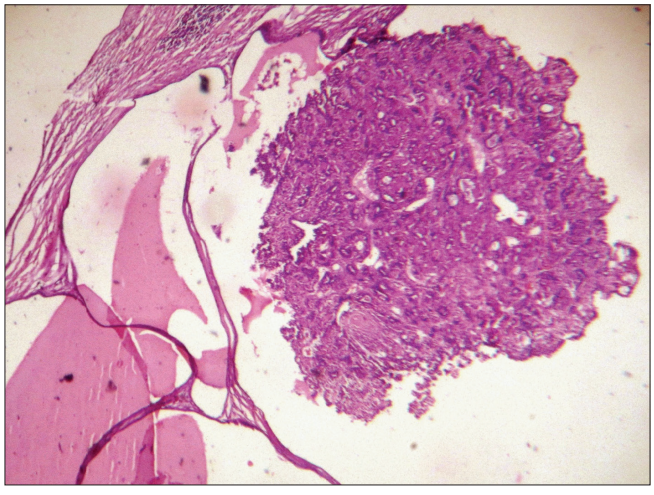

Figure 8. On histology, benign intracystic papilloma presenting as a pedunculated, broad club-like papilla stuffed with numerous glandular components (hematoxylin-eosin staining, ×40)

Ductal carcinoma was the most common malignancy, detected cytologically in 10 cases (8.7%). The hypercellular smears consisted of discohesive clusters of anaplastic epithelial cells without any bare bipolar nuclei. Four of the patients manifested ipsilateral axillary lymphadenopathy, and another patient presented with multiple subcutaneous metastases over the chest wall. Histopathology confirmed invasive breast carcinoma of no special type (IBC-NST) in nine of them, but one was found to have intraductal papillary carcinoma. Samples of a case of metaplastic carcinoma and another case of mucinous carcinoma that metastasized into the ipsilateral cervical lymph node were examined. The mucinous carcinoma yielded abundant stingy mucoid material. Atypical polyhedral epithelial cells appeared to be floating in singles or strips within the pool of extracellular mucin. Tumor cells appeared cytologically bland with prominent nucleoli and abundant cytoplasm. "Chicken-wire" blood vessels were also apparent (Figure 10). Histopathology correlated with the cytodiagnosis of mucinous carcinoma. Cytologically, the metaplastic carcinoma featured cohesive fragments of poorly differentiated malignant epithelial cells. Keratinized squamous cells were sparsely present. Nuclear pyknosis and spindly nuclear contour were also noted sporadically. The background appeared muddy with sufficient necrosis and inflammatory debris (Figure 11). Excision biopsy identified the tumor as basaloid squamous cell carcinoma (SCC) (Figure 12).

Four (3.5%) of the cases were classified into a less definitive category, as proliferative breast disease with atypia. Hypercellularity, significant nuclear crowding, and overlapping were invariably present in these smears. Additionally, cellular dyshesion, atypia, and scarcity of bipolar

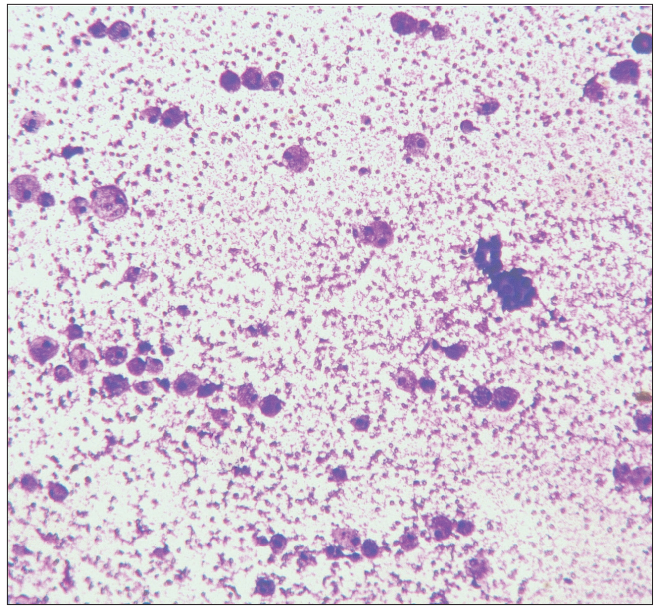

Figure 9. Mammary duct ectasia in an 8-month-old infant expresses siderophages, blood components, and occasional epithelial sheets (Leishman-Giemsa staining, ×100)

nuclei were present (Figure 13). On excision biopsy, two of the cases came out as IBC-NST and the rest as intraductal papilloma (Figure 14) and FCC (Figure 15).

Adequate diagnostic material could not be obtained in five cases (4.3%) even on repeated attempts. Four of them were treated successfully based on symptomatology. A patient underwent surgical excision, which revealed a gynecomastia. Considering all cases (i.e., benign, atypical, and malignant), no false-positive case was recorded in this study; hence, the sensitivity, specificity, negative predictive value, and positive predictive value were 100%, 91.7%, 100%, and 87.5%, respectively.

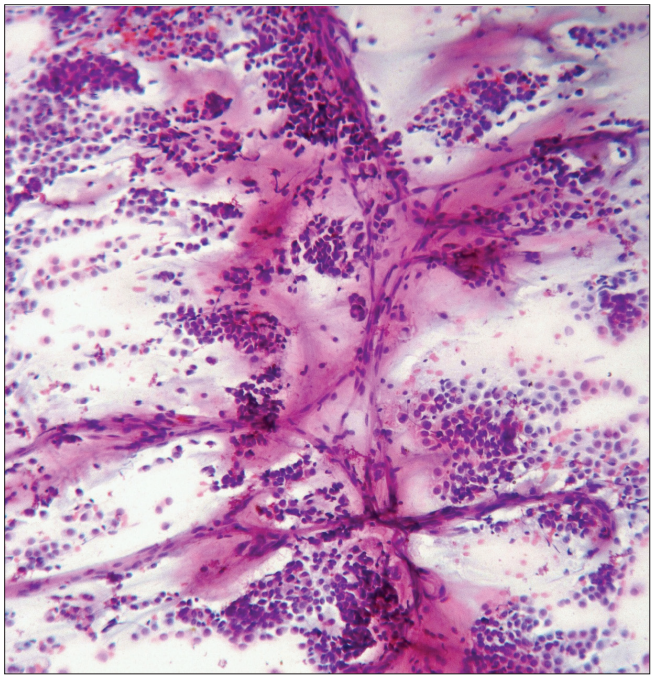

Figure 10. Cytomorphology of mucinous carcinoma: isolated polyhedral malignant cells and "chicken-wire" vascular fragments floating amidst pool of extracellular mucin (Papanicolaou staining, ×100)

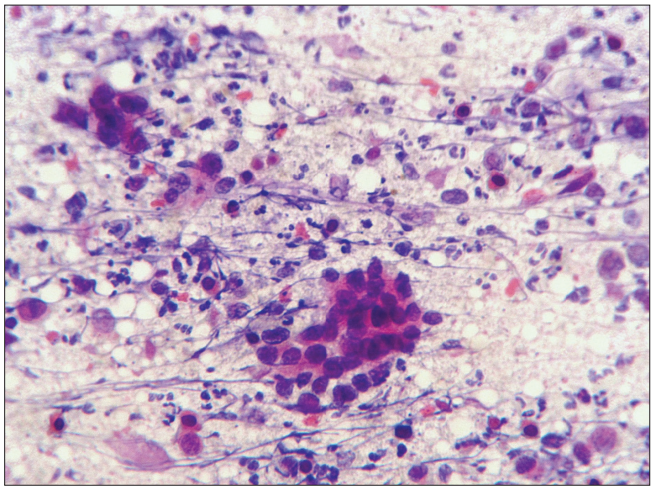

Figure 11. Cytomorphologically, clustered undifferentiated tumor cells within ample necro-inflammatory debris along with well-differentiated malignant squamous cells featuring nuclear pyknosis and cytoplasmic orangeophilia suggestive of metaplastic breast carcinoma (Papanicolaou staining, ×400)

Discussion and Conclusion

Gynecomastia is the most common male breast pathology. Its prevalence, among men with breast-related ailments, varied from 51.2% to 100% across the continents (6, 7). Asymptomatic gynecomastia is present in 60%-90% of neonates, 50%-60% of adolescents, and up to 70% of men aged 50-69 years (8). FNAC generally features mild-to-moderate cellular yields. Cytomorphologically, the sheets of bland epithelial cells, bipolar bare nuclei, and stromal fragments resemble the fibroadenoma in women (9). However, unlike fibroadenoma, majority of gynecomastia cases are cured by tamoxifen or raloxifene therapy. Therefore, a pretherapeutic cytological diagnosis of gynecomastia is important to differentiate it from other pathologies that actually need surgery and hence to avert unnecessary operative intervention (2, 8).

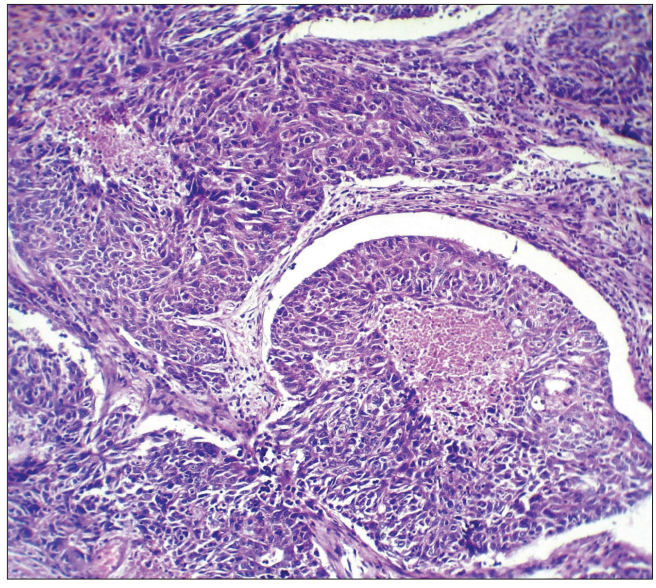

Figure 12. Basaloid variant of squamous cell carcinoma-representative of the cytodiagnosis of metaplastic carcinoma shown in Figure 11 (hematoxylin–eosin staining, ×100)

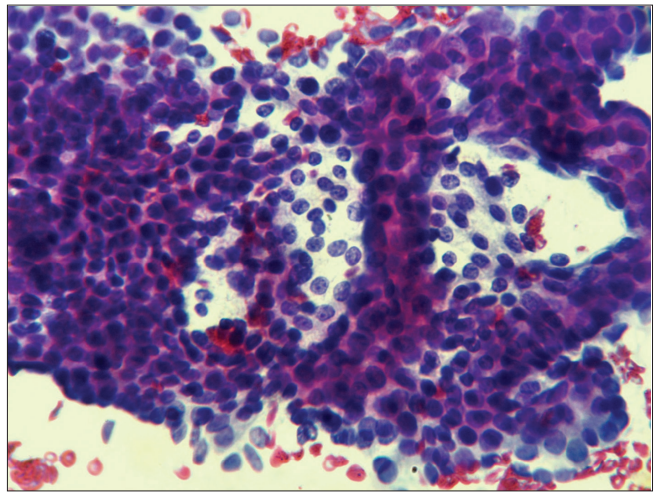

Figure 13. Proliferative breast disease with atypia on cytology: Epithelial cells forming cribriform and crowded overlapping clusters with slight nuclear irregularities, prominent nucleoli (Papanicolaou staining, ×400)

Male breasts are rarely affected by inflammatory lesions. Only 2% of their pathological conditions result from inflammation (1). Its predisposing factors include decreased immunity, older age, smoking, iatrogenic procedure, trauma, diabetes mellitus (DM), coexistent human immunodeficiency virus infection, overlying skin infection, and alpha-1 antitrypsin deficiency. Common causative organisms are *streptococci*, *staphylococci*, and *tuberculosis* (10). Pyogenic organisms are normal skin inhabitants. They gain access into the breasts either directly through the nipple or extend secondarily from any cutaneous infection (10, 11). In this study, four of the lumps were cytologically recognized as suppurative mastitis/abscess. Any history of trauma or pre-existent skin infection was negative. Therefore, retrograde spread via the nipple or secondary extension from any subclinical skin infection likely induced the condition.

India has the highest burden of tuberculosis worldwide, as 27% of global patients are living here, making prevalence for pulmonary tuberculosis as 295.9 cases per 1 lakh population. Among Indian men, the prevalence is much higher at 418.4 cases per 1 lakh population (12). Still, tuberculous mastitis is a rare disease among Indian men. Given its nonspecific clinical presentation, tuberculous mastitis is often confused with gynecomastia or breast carcinoma at the initial stage. Breasts are only secondarily infected with tuberculosis, even if its primary focus remains clinically not apparent (13). Majority of the patients acquire mammary infection through retrograde lymphatic spread via the axillary nodes from any pulmonary primary disease. Similar pathogenic route can also be followed through the tracheobronchial, paratracheal, and cervical lymph nodes. Direct extension from the lungs has also been observed along the involvement of the thoracic bone-cartilage, chest wall, etc., to the breasts. Hematogenous dissemination is mostly observed in patients with human immunodeficiency virus /acquired immune deficiency syndrome (14). In this study, the four patients with tuberculous mastitis belonged to the fragile age cluster of 55–75 years. A calcified focus from previously healed pulmonary tuberculosis was identifiable in each case. Two of the patients were simultaneously suffering from axillary tuberculous lymphadenitis. Cytological demonstration of acid-fast bacilli clinched their diagnosis.

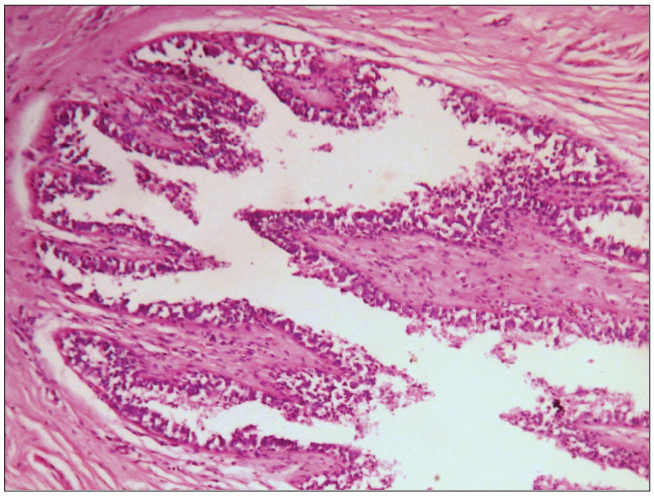

Figure 14. Corresponding histomorphology of an intraductal papilloma: Bilayer epithelial-myoepithelial cells covering the fibrovascular cores (hematoxylin-eosin staining, ×40)

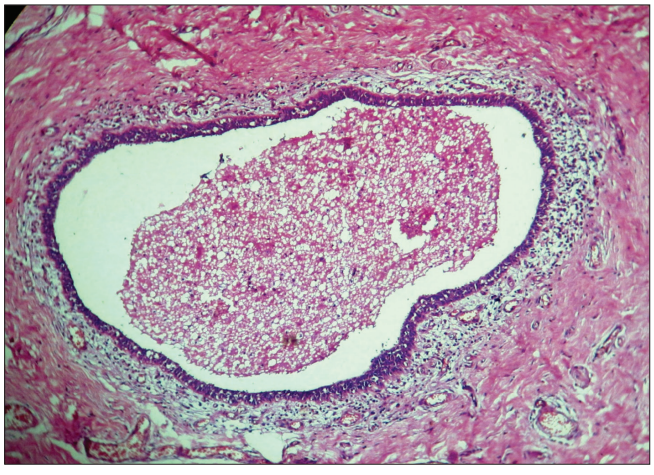

Figure 15. Histology of fibrocystic changes expressing cyst formation and pericystic chronic inflammation (hematoxylin-eosin staining, ×40)

In this study, two cases were cytologically diagnosed as chronic nonspecific mastitis. One of the patients with insulin-dependent DM underwent excision of the lump because of its refractoriness to conventional therapy. On histopathology, it showed ductular atrophy, periductular lymphocytic infiltrates, and dense collagenous fibrosis. Such histomorphology is consistent with lymphocytic mastopathy. This condition is often referred to as diabetic mastopathy due to its predilection for them. However, similar mammary pathology is encountered in other autoimmune disorders, such as systemic lupus erythematosus, Sjogren syndrome, and Hashimoto thyroiditis. It usually occurs in young to middle-aged individuals. Clinicoradiologically, the lumps resembled gynecomastia. No specific cytological features of lymphocytic mastopathy were found. FNAC is indicated for recurrent cases or for monitoring purposes after definitive therapy. Aspirates are generally paucicellular, comprising of clustered benign epithelial cells, lymphocytes, and fibroblastic stromal fragments (14). This case also clinically masqueraded as gynecomastia. FNAC yielded only scant lymphohistiocytic cells without any epithelial cells, which led to the interpretation of chronic nonspecific mastitis. Finally, on histopathology, a definite diagnosis was made.

In this study, lumps were cytologically depicted as proliferative breast disease with atypia. The diagnostic terminology "proliferative breast disease with atypia" represents the "gray zone" in breast cytology. Proper interpretation of this "gray zone" is both difficult and confusing either qualitatively or quantitatively. When the cytological specimen is cellular, with epithelial cells arranged in crowded overlapping groups, with or without any other feature of atypia-like cellular dyshesion or anaplastic changes or scarcity of bare bipolar nuclei, it is predictive of "gray zone" cytomorphology. Pathological lesions amenable to such characterization may range from proliferative fibrocystic disease or sclerosing adenosis to carcinomas (15, 16). The National Cancer Institute cytologically classifies the breast lesions as inadequate (C1), benign (C2), atypical probably benign (C3), suspected malignancy (C4), and malignant (C5). C3-C4 lesions are equivalent to the "gray zone" cytology, where a straightforward diagnosis is not provided. Histopathological evidence of malignancy is detected in 36%–52% of C3 lesions and in 81%-87.5% of C4 lesions. Still, many researchers prefer a single equivocal terminology to address both these categories (17). MacIntosh et al. (18) called these lesions collectively as "atypical." The only such lesion from their study was proved to be an invasive ductal carcinoma. In a large study of both male and female patients, Pandya and Shah (16) encountered 21 lesions of proliferative breast disease with atypia, 12 of which were biopsied and 75% of it came out as ductal carcinoma. In the present study, the "gray zone" lesions were also interpreted as "proliferative breast disease with atypia."

Histopathology findings confirmed two of these as IBC-NST and one case each of intraductal papilloma and FCC.

Fibrocystic disease is a nonspecific cytodiagnosis. Pathogenically, it originates from lobular units, so the ductules-only male breasts are rarely affected. Its pathogenesis is also poorly understood in men, which can be due to hormonal imbalance, paraneoplastic syndrome, or an idiopathic phenomenon. Most FCC cases were associated with gynecomastia, as bilateral tender and knotty swellings (19). Representative cytological samples display cohesive sheets of benign epithelial cells often featuring apocrine changes, few foamy macrophages, and thin proteinaceous fluid in the background (20). An identical cytomorphology was recapitulated in one of the patients in this study. Upon the diagnosis of bilateral FCC, he was managed conservatively. However, focal epithelial hyperplasia and atypia are commonly associated with FCC. Sometimes, on cytology, these changes appear worrisome to make it indistinguishable from malignancy. Excisional histopathology helps in diagnostic confirmation (21). The same dilemma resurfaced during the study period, as another patient with unilateral FCC was interpreted as having proliferative breast disease with atypia on initial cytology. The classic fibrocystic cytomorphology coexisted along some cell-rich overlapping aggregates of epithelial cells featuring mild nuclear irregularities and occasional mitotic figures. Histology confirmed the lesion as FCC, though some cysts were focally lined by hyperplastic epithelium with marginal nuclear atypia. No evidence of coexistent gynecomastia or any other pathology was detected.

Well-defined cytological features of benign breast papilloma-like fibrovascular stalks covered by columnar cells, large epithelial sheets with ruffled borders, and metaplastic apocrine cells were found. In contrast, other papillary-like proliferations consist of complex bulbous epithelial projections and lack the true fibrovascular cores. Still, on smear examination, difficulty often arises in distinguishing benign papillomas from any other epithelial proliferative lesion or ductal carcinoma. Almost half of the benign papillomas are therefore misdiagnosed cytologically. Smear hypercellularity, scarcity of naked bipolar nuclei, and nuclear pleomorphism are features that seldom help in excluding malignancy, as reactive atypia in papillomatous epithelia commonly play the spoilsport (22). In this study, a similar malignant case of intraductal papilloma was misdiagnosed as proliferative breast disease with atypia. It was then successfully diagnosed and cured by excisional biopsy; however, another case of intracystic papilloma was correctly interpreted on cytology. Intracystic papilloma is simply a morphological variant of intraductal papilloma. If the papillomatous duct appeared dilated and cystic, it is then diagnosed as intracystic papilloma or papillary cystadenoma. However, its treatment policy is different from intraductal papilloma (14).

Milky nipple discharge is common among neonates and infants. This physiological phenomenon is caused by a sudden drop in the level of maternal prolactin and simultaneous persistent high level of fetal prolactin. However, bloody nipple discharge is extremely rare during infancy. Generally, it lacks any association with inflammation, engorgement, or hypertrophy of the breasts. On further exclusion of any drug interaction, bleeding disorder, traumatic exposure, and underlying mass deformity, these cases are attributed to mammary duct ectasia. The specific etiology of infantile duct ectasia remains elusive. Cytology reveals variable numbers of red cells, macrophages, lymphocytes, polymorphs, and epithelial cells. Most cases resolve spontaneously within 6-9 months. Excision should be avoided, as it may cause permanent mammary deformity or dysfunction since an early age (23). Quite differently, in the presented infant, his nipple discharge subsided within 4 months of follow-up. The secretion contained mainly siderophages and blood elements, with occasional epithelial sheets. There was no other underlying pathological or biochemical abnormality as well.

The male breasts presented as the origin of 0.5%–1% of all breast malignancies in both sexes. It is responsible for <0.1% of men dying from any malignancy (24). In earlier studies on male breast pathologies, its malignant etiology was recorded in 2.5%–28.4% of the cases (1, 4, 7, 18, 20, 25). Risk factors include older age, family history of breast cancer, radiation exposure, cryptorchidism, testicular trauma, Klinefelter syndrome, liver disease, and *BRCA2* gene mutation. IBC-NST is the most common male breast malignancy. It represents approximately 85% of the cases, and this was followed by papillary carcinoma. Somehow, it occurs more often in men than in women. It constitutes approximately 5% of all breast cancers in men, compared with 1%–2% in women with breast carcinomas (24). Non-Hodgkin lymphoma, malignant melanoma, oncocytic carcinoma, secretory carcinoma, mucinous carcinoma, and metaplastic carcinoma have been rarely reported (1, 18, 20, 24-28). Metastatic involvement of male breasts with SCC and melanoma are also identified sporadically (26). In this study, a total of 14 cases (12.2%) of breast carcinoma were detected. Therefore, cytology diagnosed 10 cases as ductal carcinoma, single case each as metaplastic carcinoma and mucinous carcinoma, and two cases as proliferative breast disease with atypia. Under histopathology, a case of ductal carcinoma was confirmed as intraductal papillary carcinoma. This cytological misappropriation for an uncommon subtype of breast carcinoma has been reported quite often in men. Given their extreme rarity compared with conventional IBC-NST, they are easily misdiagnosed as ductal carcinoma on FNAC. The same fallacies were reported by MacIntosh et al. (18) for papillary carcinoma and secretory carcinoma as well as by Pailoor et al. (20) with oncocytic carcinoma.

Metaplastic carcinoma refers to a group of neoplasms that are characterized by the coexistence of adenocarcinoma with metaplastic spindle cells and/or SCC and/or areas of mesenchymal differentiation. As per the World Health Organization classification, metaplastic carcinoma is subclassified as adenosquamous carcinoma, SCC, spindle cell carcinoma, metaplastic carcinoma with mesenchymal differentiation, myoepithelial carcinoma, fibromatosis-like metaplastic carcinoma, and mixed metaplastic carcinoma (29). Histopathologically, its diagnosis is not an issue. However, a confident cytological diagnosis of metaplastic carcinoma remains a hefty task. It requires identification of dual morphology, chondroid stroma, and unequivocal malignant squamous cells or spindle cells. Clustered undifferentiated malignant epithelial cells without keratinization, fragments of amorphous metachromatic substances, atypical spindle cells, and background necrosis are the most consistent cytological findings. Multinucleated tumor giant cells, squamous differentiation, and cuboidal malignant cells are observed sporadically. However, the cytomorphology varies depending on the sampled area and the extent and type of metaplasia, therefore often leading to underdiagnoses or misdiagnoses. Amidst of similar mix-ups, Joshi et al. (30) misinterpreted nine of 10 cytological samples from metaplastic carcinomas during. Such enigma did not appear in the present report. The only case of metaplastic carcinoma expressed clusters of undifferentiated malignant epithelial cells and necro-inflammatory debris, alongside the presence of orangeophilic keratinized squamous cells that provided its definite diagnosis on

FNAC. Histopathology confirmed the tumor as basaloid SCC, without any adenocarcinoma component or mesenchymal differentiation.

In conclusion, this latest study reinstitutes the pretherapeutic utility of cytological examination in the management of pathological male breast lesions. Its major drawback present when any benign condition is associated with epithelial hyperplasia and thus expresses hypercellularity and nuclear crowding-overlapping and atypia, with scarce bipolar bare nuclei. Cytodiagnostically, such lesions are included to the quasi-specific "gray zone" category. Biopsy is mandatory for their proper classification. On a minor defection, rare subtypes of male breast cancers are often barely discernible from the conventional ductal carcinoma on cytology. Although it is of lesser importance, their individual treatment protocol is not different.

Ethics Committee Approval: This study was approved by the state ethics committee and was accomplished at the Department of Pathology, Sonoscan Healthcare, Malda, India; after acquiring approval from the State Ethics Committee (Ethics Committee Pathology 2010, Sl no: 437/L) on 7th of December, 2010.

Informed Consent: Written informed consent was procured from each patient after explicit explanation of the procedures was provided.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: K.M., R.M.; Design: R.M.; Supervision: R.M.; Materials: K.M.; Data Collection or Processing: R.M.; Analysis or Interpretation: K.M.; Literature Search: R.M.; Writing: K.M.; Critical Review: R.M.

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

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Original Article

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Angiotensin-Converting Enzyme 2 Gene Expression in Breast Tissue

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ABSTRACT

Objective: Binding to angiotensin-converting enzyme 2 (ACE2) receptor is a critical step for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to mediate its entry into target cells. ACE2 is expressed in many human tissues, including the lungs. However, no research has demonstrated that SARS-CoV-2 can infect human breast tissue. This study aimed to investigate *ACE2* gene expression in human breast tissue using a public database.

Materials and Methods: A search of a public gene expression database was performed to investigate *ACE2* gene expression in in human breast tissue.

Results: The gene expression profile demonstrated that *ACE2* gene expression was higher in human breast tissue than human lung tissue.

Conclusion: Our knowledge about coronavirus disease-2019 (COVID-19) is expanding rapidly. Clinicians are eager for vetted information regarding all aspects of this new illness, and this study demonstrates that the level of ACE2 expression in human breast tissue is higher than that in the lung tissue, a major target tissue affected by SARS-CoV-2 infection. This finding strongly suggests that SARS-CoV-2 infection causes breast pathology.

Keywords: Breast, angiotensin converting enzyme 2, gene expression, coronavirus, severe acute respiratory syndrome coronavirus 2, COVID-19

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Key Points

- SARS-CoV-2 binding to the ACE2 receptor is a critical step mediating viral entry into target cells.
- *ACE2* gene expression is higher in breast tissue than lung tissue.
- This critical discovery implies that breast tissue is directly susceptible to SARS-Cov-2 infection by the ACE2 receptor through hematogenous viral spreading following inoculation of the upper airways.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded RNA β-coronavirus (1). SARS-CoV-2, which causes the disease known as coronavirus disease-2019 (COVID-19), was first reported in late 2019 in Wuhan, China, and has rapidly developed into a pandemic and public health emergency (2-5). As of 5th October 2020, a total of 34,206,517 accumulated cases and 1,019,628 deaths have been reported worldwide, with an overall mortality rate of less than 1% (6). Researchers are integrating the rapidly emerging evidence into understanding the disease (3-9).

Angiotensin-converting enzyme 2 (ACE2) is expressed in many human tissues, including the lungs, and serves as a doorway by which the virus can enter and spread (10-12). During infection, ACE2-expressing tissues become direct targets, resulting in serious pathological changes and progressive multiple organ failure or even death in severe cases (13). Evidence has shown that, besides the respiratory injury, SARS-CoV-2 also damages the cardiac, renal, hepatic, and neurological systems (14). The influence of SARS-CoV-2 on the breast is limited and needs further investigation. This article aimed to search a gene expression database to find ACE2 expression in human breast tissue.

Materials and Methods

A search of the Gene Expression Profiling Interactive Analysis 2 (GEPIA2) database was performed to investigate ACE2 expression in human breast tissues (15). Ethical approval was not required as the study exclusively used publicly available data. The resource database from Genotype-

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Tissue Expression (version 8 data release) integrates the expression data of 11,688 normal tissue samples covering 54 tissue types to comprehensively annotate the expression patterns of each gene. Human samples are aligned against the *GRCh38* human reference genome. The GEPIA2 search of the Genotype-Tissue Expression data provided public RNA sequencing data of ACE2 expression. A differential expression analysis was performed on the selected ACE2 dataset to dynamically obtain differentially expressed genes in log2 (TPM + 1) transformed expression data. The transformed expression data from all tissue samples available were plotted using the box plots available from the GEPIA2 website with plots shown as median and 25th and 75th percentiles.

Results

The gene expression database included ACE2 expression profile. The gene expression profile demonstrated that *ACE2* gene expression was present in human breast tissue and was higher in breast tissue than in lung tissue (Figure 1).

Discussion and Conclusion

SARS-CoV-2 infection followed by COVID-19 is robust in cells expressing ACE2 receptor, a type I integral membrane protein, which controls cardiac and kidney functions by negatively regulating renin-angiotensin systems (10, 11). This study demonstrates that *ACE2* gene expression in human breast tissue is higher than in lung tissue, the major initial target tissue affected by SARS-CoV-2 infection. This is a critical discovery as these tissues may be susceptible to SARS-CoV-2 infection through the ACE2 receptor, which strongly suggests that SARS-CoV-2 infection may cause breast pathology. High ACE2 expression (e.g., in bronchial airway epithelium) may augment viral infection in patients with COVID-19 and has been demonstrated to contribute to COVID-19 morbidity and severity patterns, but studies have not looked at other tissues (9, 12, 16). Moreover, *ACE2* gene receptor expression is positively regulated in COVID-19 (16).

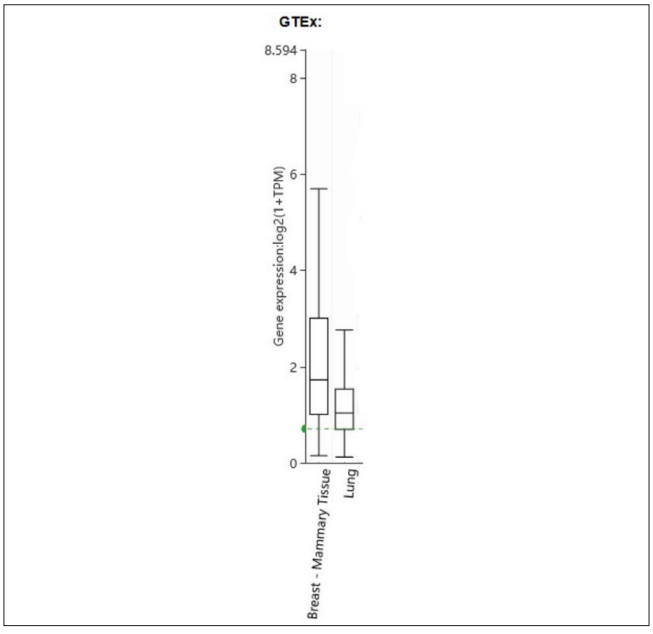

Figure 1. *ACE2* gene expression in human breast tissue and human lung tissue

ACE2: Angiotensin-converting enzyme 2; TPM: Transcripts per million

Most patients with COVID-19 present with extramammary-related manifestations of COVID-19, such as respiratory symptoms and pyrexia, and little is known about breast-related manifestations of the infection (13, 14). The outbreak of SARS-CoV-2 is still ongoing, and therefore the data on human breast tissue infected by SARS-CoV-2 are limited. At present, no certain direct impact of COVID-19 on the breast has been reported. Despite this, retrievable SARS-CoV-2 ribonucleic acid has been discovered in colostrum and breast milk using SARS-CoV-2 reverse transcriptase polymerase chain reaction examination up to four days postpartum (17-20). The implications of retrievable SARS-CoV-2 ribonucleic acid in human colostrum and breast milk remain unclear, regarding whether this translates to viable virus or degraded residual nucleic acid.

The local renin-angiotensin system importantly contributes to carcinoma micromilieu and influences carcinoma cell proliferation, infiltration, angiogenesis, and metastatic activities (21, 22). As a component of the renin-angiotensin system, ACE2 converts angiotensin II to angiotensin (1–7) (9). It is recognized that the renin-angiotensin system plays a strategic part in the adaptation of many physiological bodily functions (9). Emerging data suggest that the local renin-angiotensin system is an important component of the carcinoma micromilieu and plays a strategic part in the positive regulation of carcinoma cell proliferation, angiogenesis, metabolism, spread, and infiltration (21, 22). Meanwhile, the ACE2/angiotensin (1-7)/MAS axis plays a strategic part in positive regulation of exiguous, antiangiogenic, and antimetastatic actions (23).

The ACE2 protein expression levels in invasive breast carcinoma cells with lymphatic or distant metastasis spread and highly metastatic breast carcinoma cells are significantly lower than in neighboring breast cells, invasive ductal carcinoma cells, or low metastatic invasive breast carcinoma cells (23, 24). The staging and metastatic status of invasive breast, gallbladder, lung, pancreatic, and metastatic prostate carcinomas are negatively associated with ACE2 protein expression (23-29). Angiotensin (1-7) therapy or ACE2 protein overexpression decreases invasive carcinoma cell growth, local infiltration, and metastasis in breast invasive carcinoma, lung adenocarcinoma, and metastatic prostate carcinoma (23-29). Alternatively, invasive carcinoma cell growth, local infiltration, and metastasis of human breast adenocarcinoma are augmented in human breast adenocarcinoma cells with *ACE2* gene deactivation, but they are set free with angiotensin (1-7) therapy (23). Moreover, an angiotensin (1-7) receptor antagonist can block the effect of angiotensin (1-7) therapy or ACE2 overexpression (23). It is therefore evident that the ACE2/angiotensin (1-7)/Mas pathway acts to safeguard in a protective role, which counters both local infiltration and distant spread from invasive breast carcinoma (23, 24).

Although the precise system whereby the ACE2/angiotensin (1-7)/Mas pathway modifies invasive breast carcinoma growth, vascularity, infiltration, and metastasis is not fully known, store-operated calcium entry is crucial for the spread and infiltration of carcinoma cells by controlling cytoskeletal dynamics and organization and initiating the applicable signaling pathway for local infiltration and distant spread (30,31). Store-operated calcium entry is induced by AngII (32); ACE2 overexpression protein significantly reduces store-operated calcium entry activity (23).

Negative regulation of the ACE2/angiotensin (1-7)/Mas pathway promotes invasive breast carcinoma local infiltration and distant spread

through the activation of store-operated calcium entry pathways, which decreases E-cadherin expression (23, 24). As the *ACE2* receptor gene expression in lung tissue is dysregulated in COVID-19, it is possible that patients with invasive breast carcinoma that highly express ACE2 may have worse outcomes when infected by SARS-CoV-2 (15).

ACE2 gene expression is higher in the breast than in the lungs, and breast pathologies may ensue (33-36). This is a critical discovery as SARS-CoV-2 infection may directly and indirectly affect the breast in addition to the lungs by the ACE2 receptor.

Ethics Committee Approval: Ethical approval was not required as the study exclusively used publicly available data.

Informed Consent: This study exclusively used publicly available data.

Peer-review: Externally peer-reviewed.

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Original Article

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Validity and Reliability of the Turkish Version of the Breast Cancer Screening Beliefs Scale

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ABSTRACT

Objective: Breast cancer is an important public health problem because of its frequent occurence and fatal consequences. Early diagnosis of breast cancer increases the treatment success and survival. For the early diagnosis of breast cancer, women's screening beliefs and attitudes need to be determined. This study aimed to examine the reliability and validity of the Breast Cancer Screening Beliefs Scale to determine patients' beliefs and attitudes regarding breast cancer screening.

Materials and Methods: This methodological study was carried out with 261 women. A survey form and the Turkish version of the Breast Cancer Screening Beliefs Scale were used in the data collection. Coverage validity was determined by the coverage validity index, and the Davis technique, item-total score correlations, Cronbach alpha evaluation, factor analysis, and AMOS analysis were used.

Results: The factor structure of the 13-item Turkish version of the Breast Cancer Screening Beliefs Scale was examined. After the factor analysis, a three-factor structure emerged which accounted for 70% of the total variance and has an eigenvalue of over 1.00. In the internal consistency analyses of the scale, item-total score correlation values ranged from 0.37 to 0.90, and no items were extracted from the scale.

Conclusion: The Turkish version of the Breast Cancer Screening Beliefs Scale was found to be a valid and reliable measurement tool in determining the screening beliefs and attitudes of women.

Keywords: Women, breast cancer, screening, belief, attitude

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Key Points

- Breast cancer is the most common type of cancer in women and breast cancer screenings are very important for early detection of cancer.
- Inappropriate beliefs of women that might prevent breast cancer screening need to be determined.
- The Breast Cancer Screening Beliefs Scale is a valid and reliable measurement tool that can measure women's beliefs about breast cancer screening.

Introduction

Worldwide, the second most common type of cancer after lung cancer is breast cancer. Each year, approximately 1.38 million women have breast cancer, and approximately 458,000 women die from it. Breast cancer affects approximately 15,000 women each year in Turkey, constituting 20%–25% of all cancer cases among women. According to the Global Cancer Incidence, Mortality and Prevalence study in 2008, the incidence of breast cancer varies from 19.3 per hundred thousand women in Eastern Africa to 89.7 per hundred thousand women in Western Europe (1). The incidence of breast cancer is 23 per hundred thousand worldwide, and it is 33.8 per hundred thousand in Turkey (2, 3). The incidence of breast cancer started to increase after 2008, while the mortality rate increased by 14%. At present, breast cancer is the most common type of cancer in women, and one of every four women continues to have breast cancer (4).

As with all chronic diseases, screening programs are important to raise awareness about cancer. Cancer screening programs are one of the most effective methods to fight cancer. If it is detected at an early stage through screening, breast cancer is fully treatable. Turkey follows the World Health Organization's (WHO) recommendations for cancer screening. Women participate voluntarily in these screening programs. They are consulted about monthly breast self-examination, a clinical breast examination is performed annually, and women aged 40-69 years undergo mammography every 2 years (5).

This study was presented in the 1st International Congress on Nursing and Innovation (May 4th-5th, 2018, İstanbul) as an oral presentation.

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Turkey offers community-based cancer screenings through a total of 208 cancer early diagnosis screening and education centers, with at least one in each of the country's 81 provinces. In addition, community health centers, mother and child health and family planning centers, and family health centers have provided great support for screening in recent years. In 2016, approximately two million people were included in breast cancer screening programs, an increase compared with that in 2015 (6). Although all women were requested to be involved in this program, only 35% were screened for women cancers. To increase these rates, nurses working at relevant centers can contribute positively by organizing informative programs for breast cancer screening. Women need health education and incentive programs to change their beliefs and attitudes toward screening.

Faith or attitude is a state of being ready to show a certain viewpoint toward a situation, event, object, or person. Social experiences are learned by experience and shaped by the influence of cultures. It may lead to positive or negative behaviors. Given its abstract nature, it cannot be observed directly. Behavior can be predicted by measuring individuals' behaviors and the behaviors that serve as the controlling forces behind them. However, it is difficult to measure attitudes by observing an individual's behavior or by examining their physiological responses. For this reason, there are scales for measuring beliefs or attitudes, in which responses are usually assessed by individuals using a series of sentences or adjectives. To our knowledge, no tool has been established to measure women's beliefs about breast cancer screening in Turkey.

The purpose of this study was to adapt the Breast Cancer Screening Beliefs Scale (BCSBS) to Turkish and to make it valid and reliable.

Materials and Methods

Design and participants

This methodological study was conducted to examine the validity and reliability of the BCSBS. Women aged >20 years who presented to three family health centers in eastern Turkey from October 2017 to December 2017 comprised the study population. In adapting a scale to another culture, it is necessary to reach a group 5–10 times as large as the number of scale items (7-9). This study included 13 scale items. Sample selection was not performed, and 206 female participants who presented to the relevant centers and agreed to participate in the research formed the sample group.

Data collection and data collection tools

Research data were collected through face-to-face interviews with women using the personal information form and the Turkish version of the BCSBS.

Definitive property form: The researcher-prepared form, based on information from the literature, contains 44 questions that establish women's identities, pregnancy histories, family characteristics, and knowledge about breast cancer.

BCSBS: The scale was developed by Kwok et al. (10) in 2010 to identify women's breast cancer screening beliefs. It consists of 13 items. Each item on the original scale can be rated as one of five Likert options, ranging from "strongly disagree" (1 point) to "strongly disagree" (5 points). The scale consists of three subdimensions. The attitude subscale for health screenings consists of items 1–4, the breast cancer information and perceptions subscale consists of items 5–8, and the obstacles to mammography screening subscale consists of items 9–13. When the scale score mean was calculated, the scores were converted as 1–0, 2–25, 3–50, 4–75, and 5–100. After the conversion process, the mean score of each subscale was obtained by dividing the sum of the subscale item scores by the number of items. There were no reverse items in the scale. The lowest score taken from the scale was 0, and the highest score was 100. The mean scores of subscales >65 indicated that the screening beliefs increased positively, information status increased, and obstacles to mammography screenings decreased. The internal consistency coefficients (Cronbach's alpha) for the subscales of the original scale are between 0.76 and 0.79.

Evaluation of data

The SPSS version 23 program was used to evaluate the data. For the adaptation of the scale to Turkish and validity-reliability analysis of the scale, the process steps in the WHO's guide to the translation and adaptation of scale tools were followed (11). Reliability of the scale was assessed by item analysis, Cronbach's alpha value, and test-retest correlation. Exploratory analyses were performed to test the factor structure validity of the scale. AMOS analysis were performed to confirmatory factor analyses. Appropriateness of the data for the factor analysis was assessed using the Kaiser-Meyer-Olkin (KMO) value and Bartlett's test of sphericity. Descriptive data were calculated by number, percentage, mean, and standard deviation. Statistical significance level was determined with $p<0.05$.

Ethics of research

To develop the Turkish version of the BCSBS, written permission was obtained from Cannas Kwok through electronic mail. The approval of the Atatürk University Faculty of Nursing Ethics Committee was obtained before conducting the study (no: 2016-6/12, date: 2016/05/01). Verbal consent was taken after the participants were informed of the purpose of the investigation and the purposes for which the results were to be used.

Results

Of the study participants, 39.1% were 18–24 years old, 64% were married, and 59% lived in the province center. In addition, 36% of the participants were primary school graduates, 83.5% were not employed, and 66.3% reported having moderate income.

Language and content validity

The translation/back-translation method was used for the language validity of the BCSBS. Three people, which included a linguist and two field specialists, translated the original English version of the scale into Turkish. These translations were examined by the researchers and turned into a single common form. The resulting form was translated back into English by a different linguistic expert who is fluent in both Turkish and English. The original scale items and scale items that were translated/back-translated were compared, and results revealed the meanings of the scale items were not changed. Finally, the clarity of the scales was checked by a Turkish language expert. Results of these studies confirm that the Turkish form of the BCSBS is a suitable measuring tool in terms of language validity.

The Davis technique was used to assess content validity. The Turkish version of the BCSBS was presented to eight leading expert academicians. They were asked to evaluate each item in terms of

language suitability and intelligibility for the Turkish community, with scores ranging from 1 to 4 (4: very appropriate; 3: appropriate but small changes are needed; 2: appropriate to be included in the article; 1: not appropriate). For the evaluation of each item, the content validity index for each item was calculated by dividing the number of experts who marked option (3) or (4) by the total number of experts, and the content validity index was accepted as 0.80 (7, 9, 12). In this study, no items were removed because no item had value <0.80.

Reliability analysis of BCSBS

For material analysis and internal consistency, Cronbach's alpha reliability analyses were performed for the 13 items in the BCSBS. Table 1 shows the item-total score correlations of the scale. These correlations ranged from 0.46 to 0.57. No items were removed because there was no change in the Cronbach's alpha values when any item was removed; the item-total score correlations were not below 0.20 (Table 1).

The Cronbach's alpha value of the internal consistency reliability coefficient of the scale was 0.86. The Cronbach's alpha values that served as reliability coefficients of the subscales were as follows: attitude to health check-up, 0.86; breast cancer knowledge and perceptions, 0.81; and barriers to mammography screenings, 0.83. The average scores of the subscales were as follows: attitude to health check-up, 41.93±26.51; breast cancer knowledge and perceptions, 68.60±22.93; and barriers to mammographic screening, 66.46±22.19.

Test-retest reliability

To determine the reliability of the scale, a retest was administered to 66 people 2 weeks later. The correlation value between the first and second measurement results was r = 0.842, and p<0.001 was the significance level. This finding suggests that the first and second measurement results of the scale applied at 2-week intervals are comparable.

Validity analysis of BCSBS

Bartlett's test was applied to determine whether the relationships between the KMO test and variables to be analyzed were significant and non-zero and to determine whether data were applicable for the factor analysis. The KMO coefficient was 0.77, the chi-square value of Bartlett's test was also significant at the advanced level (p<0.001), and results revealed that the data were appropriate and sufficient for the factor analysis.

To reveal the factor structure of the 13-item BCSBS, principal component analysis and a varimax rotation method from the factor analysis methods were applied, and a three-factor structure that explains 65% of the total variance and has an eigenvalue above 1.00 emerged. Factor loadings of the items ranged from 0.59 to 0.86 (Table 2). The distribution of the 13 items constituting the three-factor structure of the BCSBS by factors was similar to that of the original:

1. Subscale: This factor consists of a total of four items (items 1–4), and it was named the "attitude to health check-up" subdimension as its original was.

2. Subscale: This factor consists of a total of four items (items 5–8), and it was named the "breast cancer knowledge and perceptions" subdimension as its original was.

3. Subscale: This factor consists of a total of five items (items 9–13), and it was named the "barriers to mammographic screening" subscale as its original was.

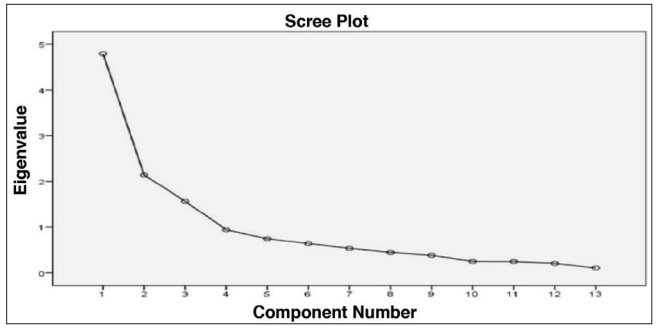

Figure 1. Scree plot test

Table 1. Internal consistency and homogeneity of the Breast Cancer Screening Beliefs Scale

Items	Average of scale if item is removed	Variance of scale if the item is removed	Corrected Item-total correlation	Cronbach's alpha coefficient of the scale if the item is removed
1.	41.3	73.6	0.52	0.85
2.	41.1	73.8	0.52	0.85
3.	41.5	75.1	0.47	0.85
4.	41.4	73.9	0.54	0.84
5.	40.2	74.7	0.57	0.84
6.	40.0	76.7	0.50	0.85
7.	40.5	75.3	0.51	0.85
8.	40.3	74.0	0.52	0.85
9.	40.7	76.8	0.48	0.85
10.	40.3	77.5	0.46	0.85
11.	39.8	76.2	0.51	0.85
12.	40.5	73.4	0.55	0.84
13.	40.4	73.1	0.55	0.84

Analysis of the factor structure of the BCSBS revealed that the first, second, and third factors explained 23.2%, 22%, and 20.2% of the total variance, respectively, and all these factors combined explained 65.3% of the total variance.

In the Scree plot test result graph, the first sudden change of the eigenvalue >1.00 occurred in the third factor, and based on this result, the scale would consist of three factors. The Scree plot test result is presented in Figure 1.

Confirmatory factor analysis (CFA) was performed to determine whether the three-factor structure of the scale was confirmed. A number of compliance indices were used to demonstrate the adequacy of the tested model in CFA. The chi-square test for the goodness of fit index (GFI), root mean square error of approximation (RMSEA), root mean square residual (RMR), comparative fit index (CFI), normed fit index (NFI), and adjusted goodness of fit index (AGFI) compliance indices for the CFA in this study were examined.

According to the results of the CFA, the values were detected as χ^2 = 157.09, standard deviation (SD) = 57.12, and p = 0.000; χ^2/SD = 2.75, which is within the acceptable reference value range ≤5. This finding also suggests that the data are compatible to the model, and results of other indices tests were as follows: RMSEA = 0.093, NFI = 0.890, CFI = 0.926, RMR = 0.10, GFI = 0.89 and AGFI = 0.84. These findings show that the model-data compatibility is acceptable. In other words, the three-factor model is appropriate and provided the construct validity of the scale. First-level CFA results are shown in Figure 2.

Discussion and Conclusion

For material analysis and internal consistency, Cronbach's alpha reliability analyses were performed for 13 items in the BCSBS. The Cronbach's alpha coefficient was calculated to determine the internal consistency of Likert-type scales. The Cronbach's alpha coefficient is a weighted standard deviation mean found by the estimate of the total of the variances of the items in the scale to the general variance. A high Cronbach's alpha coefficient of a scale indicates that it consists of coherent items that measure the same items of the scale (8, 13).

In the literature, when the Cronbach's alpha coefficient range is $0.00<\alpha<0.40$, the scale is unreliable; when the coefficient range is $0.40<\alpha<0.60$, the scale is quite reliable; and when the coefficient range is $0.60<\alpha<0.80$, the scale is highly reliable (13, 14). In this study, the Cronbach's alpha coefficient of the Turkish version of the BCSBS was 0.86. The Cronbach's alpha values of each subdimension of the scale were as follows: attitudes toward health screenings, 0.86; information and perceptions about breast cancer, 0.81; and barriers to mammographic screening, 0.83. A study reported that the original scale has a Cronbach's alpha coefficient of 0.70 and the subscales have 0.76–0.79 (10). These coefficients are close to each other. The range of the Cronbach's alpha coefficients of the Turkish version of the scale and its subscales is $0.80<\alpha<0.100$, which may mean that the scale is highly reliable.

Another internal consistency criterion is the item-total correlation. In this method, the variance of a scale item and the variance of total scale score are compared, and the relationship between them is examined

Table 2. Factor structure, exploratory variance values, and Eigen, values of the scale

Factors	Items	Factors loading		
Attitude toward health screening	If I feel well, it is not necessary to have a health check-up	0.85	-	-
	If I follow a healthy lifestyle such as a balanced diet and regular exercise, I do not feel it is necessary to have a regular health check-up	0.77	-	-
	I see a doctor or have my health check-up only when I have a health problem	0.86	-	-
	If I feel healthy, I do not need to see the doctor	0.84	-	-
Breast cancer knowledge and perceptions	Breast cancer is like a death sentence; if you get it, you will surely die from it	-	0.82	-
	Breast cancer cannot be cured; you can only prolong the suffering	-	0.80	-
	Even if breast cancer is detected early, there is very little a woman can do to reduce the chances of dying from it	-	0.81	-
	If a woman is fated to get breast cancer, she will get breast cancer; there is nothing she can do to change fate	-	0.64	-
Barriers to mammographic screening	I am worried that having a mammogram will hurt my breasts	-	-	0.59
	It would be difficult to arrange transportation for getting a mammogram	-	-	0.75
	I do not want to have a mammogram because I cannot speak Turkish	-	-	0.72
	I do not want to go for a mammogram because I would need to take off my clothes and expose my breasts	-	-	0.86
	Having a mammogram is embarrassing	-	-	0.82
	Explotary variance values of factors	**Eigenvalues**		
Factor 1	23.6	3.0		
Factor 2	22.0	2.9		
Factor 3	20.2	2.6		
Total variance is 65.3%				

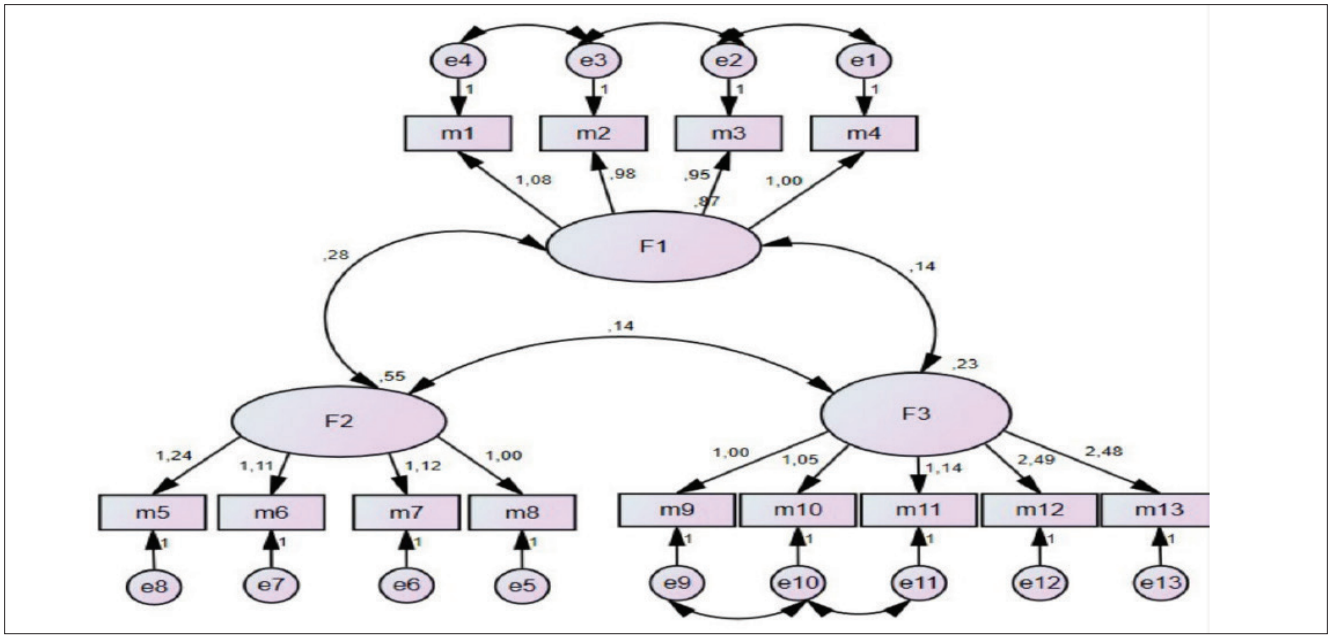

Figure 2. Confirmatory factor analysis of the Breast Cancer Screening Beliefs Scale

(13). As the item-total score correlation increases, the activity of that item increases, and when the correlation coefficient is low, the scale items are not reliable enough. In the literature, the correlation between the total score of a substance and the total score is 0.20 (15).

The item-total score correlation values of the original scale were not reported (10). In this study, the item-total score correlations ranged from 0.46 to 0.57, and the item-total score correlations of all items were sufficient. All item-total score correlations of the scale items were significant at $p<0.001$. No items were removed because there was no change in the Cronbach's alpha values when any item was removed; the item-total score correlation was not below 0.20. These findings show that there are no problematic items in the Turkish version of the 13-item BCSBS.

Test-retest reliability is a power that can give consistent results to an application without applying a measurement tool and show stability over time (8, 13). The stability of the scale is evaluated in terms of time invariance. When the same measurement tool is applied to individuals at different times, the similarity, i.e., consistency of the answers given by the individuals to the items of the measurement tool, indicates that the tool has determinedness against time (9). A correlation analysis of Pearson moment products of inertia was performed to evaluate the determinedness by time of the scale.

A study stated at least 30 individuals should be reached for the test-retest correlation analysis (16). In this study, the scale was applied to the sample group of 66 people twice at 2-week interval. The correlation value between the first and second measurement results of the scale was $r = 0.842$, and a statistically significant correlation was found between the two measurements at a significance level of $p<0.001$. This finding suggests that the first and second measurement results of the scale are comparable. The test-retest reliability analysis results were not specified on the original scale (10).

Findings from the analyses to determine the reliability of the scale indicate that the Turkish version of the BCSBS has high reliability.

Findings related to the validity analyses

Factor analysis is a process in which the subdimensions of the scale items are aggregated (17, 18). Before the factor analysis, KMO analysis was performed to determine the adequacy of the sample for the factor analysis, and Bartlett's test of sphericity analysis was performed to determine the suitability of the sample for the factor analysis.

The KMO value is excellent between 0.90 and 1.00, good between 0.80 and 0.89, moderate between 0.70 and 0.79, weak between 0.60 and 0.69, and poor between 0.50 and 0.59; if it is <0.50, it is interpreted as unacceptable (13, 14). For a good factor analysis, the KMO value must be above 0.60 (13). The KMO value of the original scale was 0.71 (10). In this study, the KMO coefficient was 0.77. When this finding was examined according to the above-mentioned KMO values, the sample size was considered sufficient for the factor analysis.

The result of Bartlett's test of sphericity in the original scale was X^2 = 1669.6% ($p<0.001$) (10). In this study, Bartlett's test result was X^2 = 1396.1% ($p<0.001$). The significance of this test suggests that the sample size is good and that the correlation matrix is appropriate for the factor (7, 13). This finding also indicates that the data are appropriate for the factor analysis.

Based on these findings, an exploratory factor analysis was conducted to reveal the factor structure of the Turkish version of the 13-item BCSBS, and the results were analyzed using the principal component method and varimax vertical rotation method (18).

After the explanatory factor analysis, a three-factor structure emerged that has an Eigenvalue >1.00 and explains 65% of the total variance. For factor analysis in the literature, the percentage of factor loadings to explain the total variance is required to be 0.40 and above (18).

Evaluation of the factor structure of the Turkish version of the BCSBS revealed that the first, second, and third factors explained 23.2%, 22%, and 20.2% of the total variance, respectively, and all these factors combined explained 65.3% of the total variance. On the original scale, three factors explain 46.8% of the total variance (10). A high ratio of

the explained variance of a scale indicates that the scale has a strong factor structure. Studies have presented that the variance rates are sufficient between 40% and 60% (13, 17, 18).

Studies have also presented that the factor loadings following factor analysis should be ≥0.30 (13, 17, 18). In this study, the factor load of the items is between 0.36 and 0.90. The reported factor loads of the 13 items on the original scale were between 0.42 and 0.85 (10). In the BCSBS, the factor load matrix was examined using the varimax rotation method to determine which items formed three factors. The matrix result of the factor load revealed the following:

Factor 1 on the original scale was composed of items 1–4.

Factor 2 on the original scale was composed of items 5–8.

Factor 3 on the original scale was composed of items 9–13.

In the factor analysis, the scale factor is determined by the Scree plot test. In that test, the factors with Eigenvalues >1 are examined by the graphical method. A study suggested selecting factors up to the first sudden change in the graph and the slope of the graphical curve obtained from this test (18). In the Scree plot test result graph, the first sudden change of the Eigenvalue above 1.00 occurred in the third factor. Considering this result, the Turkish version of the scale had three factors as in the original scale.

CFA was performed to determine whether the three-factor structure of the scale was confirmed. The results of the CFA revealed $\chi^2/SD = 2.75$, which is smaller than the acceptable reference value ≤5, and $p = 0.015$. χ^2 results test the compliance of the model data and show that the data are compatible to the model. This finding also suggests that the data are compatible to the model.

In the literature, the acceptable compliance value of the GFI, CFI, and NFI is 0.90, and the perfect compliance value is ≥0.95. The acceptable compliance value of the AGFI index is 0.85, and the excellent compliance value is ≥0.90; and the acceptable compliance value for NFI is 0.90, and excellent compliance value is ≥0.95 (19-22). The acceptable compliance value of RMSEA and RMR indices is <0.08, and excellent compliance value is <0.05.

Results of some compliance indices of the Turkish version of the scale are as follows: RMSEA = 0.093, NFI = 0.890, CFI = 0.926, RMR = 0.10, GFI = 0.89, and AGFI = 0.84. These values are in a good level of fit index. These findings show acceptable model-data compatibility. In other words, the three-factor model is appropriate, and this provided the construct validity of the scale. CFA was not performed on the original scale (10).

The Turkish version of the BCSBS, consisting of 13 items and three subscales, was found to be a valid and reliable measurement tool in Turkish society. It can be used in studies on women's beliefs about breast cancer screening and influencing factors.

Ethics Committee Approval: To develop the Turkish version of the BCSBS, written permission was obtained from Cannas Kwok through electronic mail. The approval of the Atatürk University Faculty of Nursing Ethical Committee was obtained before conducting the study (no: 2016-6/12, date: 2016/05/01).

Informed Consent: Verbal consent was taken after the participants were informed of the purpose of the investigation and the purposes for which the results were to be used.

Peer-review: Externally-peer reviewed.

Authorship Contributions

Concept: A.S.Ç.; Design: A.S.Ç.; Materials: N.T.; Data Collection and/or Processing: N.T.; Analysis and/or Interpretation: N.T.; Literature Search: A.S.Ç.; Writing Manuscript: N.T., A.S.Ç.

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Original Article

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Clinical and Pathological Characteristics of Patients with High-Risk Breast Cancer Based on BRCA Mutation Profiles: A Retrospective Study

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ABSTRACT

Objective: This study aimed to determine the differences in clinicopathological features of Turkish patients with high-risk breast cancer based on the mutation status of two breast cancer susceptibility genes (BRCA1/2) .

Materials and Methods: This study enrolled patients with invasive breast cancer who have been evaluated for BRCA1/2 mutations due to the presence of high-risk factors admitted to two tertiary referral centers in Turkey. Clinical and histopathological features were analyzed in BRCA1 mutation carriers, BRCA2 mutation carriers, and non-carriers.

Results: A total of 302 patients with a mean age of 44.2±9.9 (22–82) years were included. BRCA1/2 mutation was found in 75 (24%) patients, of whom 41 (13.6%) were BRCA1 mutation carriers and 37 (12.3%) were BRCA2 mutation carriers. Moreover, 104 (34.4%) and 4 (1.3%) patients had family history of breast and ovarian carcinoma, respectively. The rates of triple negativity (56.1%), histologic grade 3 (65.9%), and lymphovascular invasion (78%) were significantly higher in BRCA1 mutation carriers than in non-carriers and BRCA2 mutation carriers. Furthermore, 87% of triple-negative BRCA1 mutation carriers had histologic grade 3 tumors compared with 38.9% in non-triple-negative BRCA1 mutation carriers, and the difference was significant.

Conclusion: Findings of this study showed that BRCA1-related breast cancers represent a distinct group with unique pathological features, which are usually associated with a poor prognosis.

Keywords: BRCA, breast cancer, Triple-negative, lymphovascular invasion, grade

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Key Points

- The rates of triple negativity, histologic grade 3, and lymphovascular invasion were significantly higher in BRCA1 mutation carriers.
- While most of the triple-negative BRCA1 mutation carriers had histologic grade 3 tumor, it was not common in non-triple-negative BRCA1 mutation carriers.
- These findings showed that BRCA1-related breast cancers have pathological features related with poor prognosis.

Introduction

Evaluation of two breast cancer susceptibility genes, namely, *BRCA1* and *BRCA2*, is essential in patients with a predisposition to carry these mutations. Number of family members with breast cancer, young age at diagnosis, bilateral disease, and family history of ovarian cancer have been proposed as predictors of BRCA 1/2 mutations in patients with breast cancer (1). The frequency of BRCA1 and BRCA2 mutations may vary between ethnic groups (2). However, only a few studies have investigated the frequency of BRCA1/2 mutations in Turkish patients with breast cancer (3,4). Additionally, it is crucial to determine the clinical characteristics and pathological features in BRCA1/2 mutation carriers, which is also essential to define the differences between them and BRCA mutation non-carriers (5). In this study, we aimed to elucidate the frequency of BRCA1/2 mutations in a large series of patients with high-risk breast cancer and its relationship with personal/family history

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profiles and to perform clinicopathological analysis of patients with BRCA1/2-associated breast carcinoma from two tertiary referral centers in Turkey.

Materials and Methods

Among patients diagnosed with invasive breast cancer between 2015 and 2020 in two tertiary referral centers in İstanbul, patients with breast cancer who have been evaluated for BRCA1/2 mutations due to the presence of high-risk factors including younger age at diagnosis (<40 years old), male sex, bilateral localization of the tumor, and personal/family history of breast and ovarian cancer were enrolled in this study. BRCA1/2 mutations were investigated using next-generation sequencing. Patients' data including demographic information and frequency of BRCA mutation according to personal/family history risk factors were retrospectively analyzed. In addition, BRCA1 mutation carriers, BRCA2 mutation carriers, and non-carriers were analyzed in terms of the clinical and histopathological features including hormonal status, histologic grade, lymphovascular invasion, and perineural invasion.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Review Committee of İstanbul Professor Doctor Cemil Taşçıoğlu City Hospital (approval no. 48670771-514.10/210).

Statistical analysis

Data were analyzed using SPSS 22.0 software program. All continuous values were presented as median (range) and mean ± standard deviation. Categorical data were expressed as a percentage and number. Associations between patients' BRCA mutation status and demographical, clinical, and histopathological characteristics were assessed using the chi-square test. The p-value of <0.05 was considered significant.

Results

A total of 302 patients with a mean age of 44.2±9.9 (22–82) years, of whom five were male, were included in this study. Moreover, 203 (68.4%) and 94 (31.6%) female patients had premenopausal and postmenopausal states, respectively. Breast carcinoma was localized bilaterally in 21 (7%) patients, and only 6% of our patients had metastatic disease. A total of 75 (24%) patients were BRCA1/2 mutation carriers. Forty-one (13.6%) patients were BRCA1 mutation carriers, 37 (12.3%) were BRCA2 mutation carriers, and three (1%) were both BRCA1 and BRCA2 mutation carriers. First-/second-degree relatives of 104 (34.4%) and 4 (1.3 %) patients had history of breast and ovarian carcinoma, respectively. Additionally, the frequency of BRCA mutation was the highest in patients with breast carcinoma with a family history of ovarian carcinoma (75%), followed by patients with breast carcinoma with a personal history of ovarian carcinoma (62.5%), and male patients with breast cancer (60%).

Comparison of demographic, clinical, and pathological data of patients according to the BRCA mutation profile are shown in Table 1. Most of the BRCA1 mutation carriers (75.6%) were >40 years old (p<0.05). Among BRCA1 mutation carriers, 19.5%, 43.9%, and 31.7% were 30–39, 40–49, and 50–59 years of age, respectively. Among BRCA2 mutation carriers, 43.2%, 31.7%, and 5.4% were 30–39, 40–49, and 50–59 years of age, respectively. No significant difference was found among BRCA1 mutation carriers, BRCA2 mutation carriers, and BRCA non-carriers in terms of menopausal status and body mass index (Table 1).

Characteristics of patients' tumors were evaluated according to their BRCA mutation profiles (Table 1). As regards the histological type of tumors, invasive ductal carcinomas were found in 260 (86%), invasive lobular in 20 (6.6%), and other types in 22 (7.3%) patients. Disease stage, tumor histology, mean tumor size, axillary nodal status, perineural invasion, and Ki-67 proliferation index were comparable among BRCA1 mutation carriers, BRCA2 mutation carriers, and non-carriers (Table 1). However, the rate of lymphovascular invasion was significantly higher in BRCA1 mutation carriers (78%) than in BRCA2 mutation carriers (54.1%) and non-carriers (55.3%) (Table 1).

The interrelationship between the estrogen receptor (ER) status, progesterone receptor (PR) status, Her2-neu status, histologic grade, and BRCA mutation profiles of our patients was also evaluated. BRCA1 mutation carriers were more likely to be diagnosed with triple-negative breast cancer (56.1%) than non-carriers (32.2%) and BRCA2 mutation carriers (29.7%) (p = 0.01) (Table 1). ER, PR, and HER-2/neu states were comparable between BRCA1/2 mutation carriers and non-carriers. Moreover, 65.9% of BRCA1 mutation carriers had histologic grade 3 tumor, compared with 32.2% and 37.8% in BRCA non-carriers and BRCA2 mutation carriers, respectively (Table 1). The distribution of BRCA1 carriers was also evaluated according to the triple-/non-triple-negative status and histologic grade of the tumor (Table 2). Moreover, 87% of the triple-negative BRCA1 mutation carriers had histologic grade 3 tumor, compared with 38.9% of non-triple-negative BRCA1 mutation carriers, and the difference was significant (Table 2).

Discussion and Conclusion

In this study, we identified the clinical and pathological characteristics of patients based on their BRCA mutation profiles from a cohort of Turkish patients with high-risk breast cancer. We found that more cases of BRCA1-related breast cancers were triple-negative with a higher ratio of histologic grade 3 tumor and lymphovascular invasion than were BRCA-negative and BRCA2-related breast cancers, which are usually associated with a poor prognosis.

BRCA mutation carriers have a very high-risk of breast cancer by age 70, with incidence of 47%–66% (1). Overall, mutations in these genes are implicated in approximately 15% of women with familial breast cancer and a similar proportion of all women with incidental ovarian cancers (6). Because women with BRCA mutation-associated breast cancer also have an elevated risk of other malignancies, identifying these mutations is essential for genetic counseling, testing, screening, and prevention strategies (1). However, the prevalence of BRCA1/2 mutation varies based on several factors, including ethnicity, age at diagnosis, sex, tumor histology, and family history (1, 2). A few studies from Turkey have reported that the mutation prevalence in patients with high-risk breast carcinoma ranged from 14% to 19% (3, 4). In our study, the total prevalence rates of BRCA, BRCA1, and BRCA2 mutations were 24%, 13.6%, and 12.3%, respectively, among patients with high-risk breast cancer. In a study conducted in Malaysia, patients were grouped according to their personal/family history, and the likelihood of having these mutations was reported highest (60%) in patients with breast and ovarian cancer, followed by patients with

Table 1. Clinical and pathological characteristics of patients with breast cancer according to BRCA mutation status.

Characteristics		BRCA1 carriers	BRCA2 carriers	BRCA non-carriers	p-value
		n = 41 (%)	n = 37 (%)	n = 227 (%)	
Age (years)	**≤40**	10 (24.4)	19 (51.4)	105 (46.3)	0.021
	>40	31 (75.6)	18 (48.6)	122 (53.7)	
BMI (kg/m²)		28.4±5.5	28.7±6.8	27.6±5.0	0.583
Menapousal status	**Premenopausal**	28 (68.3)	26 (74.3)	151 (67.4)	0.718
	Postmenopausal	13 (31.7)	9 (25.7)	73 (32.6)	
Mean tumor size (mm)		32.9±21.3	31.9±22.1	29.2±17.2	0.618
Axillary nodal status	**Positive**	16 (42.1)	11 (39.3)	95 (49.7)	0.453
Lymphovascular invasion	**Positive**	32 (78.0)	20 (54.1)	125 (55.3)	0.022
Perineural invasion	**Positive**	28 (68.3)	18 (48.6)	114 (50.7)	0.099
Tumor histology	**IDC**	35 (85.4)	34 (91.9)	194 (85.5)	0.451
	ILC	1 (2.4)	1 (2.7)	18 (7.9)	
	Others	5 (12.2)	2 (5.4)	15 (6.6)	
Ki-67(%)	**≤5%**	1 (2.4)	2 (5.4)	20 (8.8)	0.585
	5%–20%	12 (29.3)	14 (37.8)	77 (33.9)	
	>20	28 (68.3)	21 (56.8)	130 (57.3)	
Triple-negative		23 (56.1)	11 (29.7)	73 (32.2)	***0.010***
ER	**Positive**	17 (41.5)	23 (62.2)	139 (61.2)	0.055
PR	**Positive**	15 (36.6)	19 (51.4)	113 (49.8)	0.274
Her2/neu	**Positive**	3 (7.3)	6 (16.2)	44 (19.4)	0.169
Histologic grade	**1**	2 (4.9)	0 (0.0)	11 (4.8)	***<0.001***
	2	12 (29.3)	23 (62.2)	143 (63)	
	3	27 (65.9)	14 (37.8)	73 (32.2)	
Stage	**1**	7 (17.1)	8 (21.6)	39 (17.2)	0.280
	2	22 (53.7)	14 (37.8)	115 (50.7)	
	3	7 (17.1)	12 (32.4)	63 (27.8)	
	4	5 (12.2)	3 (8.1)	10 (4.4)	

Significant p-values are shown in bold and italic.
IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; BMI: Body mass index; ER: Estrogen receptor; PR: Progesterone receptor; n: Number

Table 2. Distribution of BRCA1 mutation carriers according to the receptor status and histologic grade of the tumor

	BRCA1 mutation carriers				p-value
	Triple-negative		Non-triple-negative		
	n	%	n	%	
Grade 1	1	4.3	1	5.6	***0.001***
Grade 2	2	8.7	10	55.6	
Grade 3	20	87.0	7	38.9	

Significant p-values are shown in bold and italic.
n: Number

breast carcinoma with a family history of ovarian cancer (50%), similar to our results (7).

In the present study, no significant difference was found between BRCA mutation profile and stage, tumor histology, mean tumor size, axillary nodal status, perineural invasion, and Ki-67 proliferation index. Numerous studies have also reported that tumor size, tumor type, and axillary nodal status were not significantly different between patients according to the BRCA mutation profile, similar to our results (8-11). However, in our study, lymphovascular invasion was more often noted in BRCA1 mutation carriers (78%) than in BRCA2 mutation carriers (54.1%) and non-carriers (55.3%). A study conducted in Turkey, which evaluated the axillary nodal involvement in patients with breast cancer regardless of BRCA mutation status, reported that lymphovascular invasion occurred in 59.2% of their patients, which was lower than that in BRCA1 mutation carriers in our study (12). Additionally, a few studies have evaluated the incidence of lymphovascular invasion in patients with BRCA-related breast cancer, but did not find a significantly higher incidence of lymphovascular invasion in BRCA1 mutation carriers (8-10, 13-16). In one of these previous studies, which is a hospital-based cohort study analyzing whether tumors of patients with BRCA1-associated breast carcinomas are different from those of patients with breast cancer without BRCA mutation, the lymphovascular invasion was more common (50%) in BRCA1 mutation carriers than in non-carriers (21%), but the difference did not reach significance (8). In another study, lymphatic invasion was noted in a higher proportion (52.5% and 52.4%) of BRCA1 mutation carriers than of BRCA1 non-carriers (26.2% and 35.7%) with familial and sporadic breast cancer, respectively (16). Interestingly, in a previous study, lymphovascular invasion was more often reported (53%) in BRCA2 mutation carriers than in BRCA1 mutation carriers (39%) and non-carriers (48%) (17).

In some studies that have analyzed the distribution of hormonal status in BRCA mutation carriers, BRCA1 and BRCA2 mutation carriers were grouped together instead of being examined as two different groups, culminating with the inconsistent results (14, 18). However, in subsequent studies, when BRCA1 and BRCA2 mutation carriers were grouped separately, BRCA1 mutation carriers were more likely to be diagnosed with triple-negative breast cancer than non-carriers, and pathological characteristics were comparable between BRCA2 mutation carriers and non-carriers, similar to our results (5, 17, 19). In studies that have analyzed the relationship between BRCA mutation profile and triple-negative tumor pathology, 50%–88% of BRCA1 mutation carriers were diagnosed with triple-negative breast cancer against 14.6%–34% in BRCA mutation non-carriers (17, 20-22). Additionally, in a study of a large group of patients with breast cancer, triple-negative breast cancer was diagnosed in 57.1%, 23.3%, and 13.8% of BRCA1 mutation carriers, BRCA2 mutation carriers, and non-carriers, respectively (5). In our study, the ratio of patients with triple-negative cancer based on the BRCA mutation profiles was consistent with those reported in above-mentioned previous studies (5, 17, 20-22). In some studies including different ethnic groups, a hormone receptor status was evaluated in BRCA1 mutation carriers, and these patients were more likely to have ER-negative breast cancer (5, 8, 9, 17, 19). In our study, the number of ER-negative BRCA1 mutation carriers was higher than those of BRCA2 mutation carriers and non-carriers, but the difference did not reach significance.

Tumors in BRCA1 carriers had a higher histologic and nuclear grades than those in BRCA non-carriers (5, 8, 9, 17). In our study, 65.9% of BRCA1 mutation carriers had histologic grade 3 tumors compared with 32.3% and 37.8% of non-carriers and BRCA2 mutation carriers, respectively. In another study, BRCA1 mutation carriers with triple-negative disease were reported as having higher nuclear grade (grade 3, 93.5%) than non-triple-negative BRCA1 mutation carriers (grade 3, 75%) (5). In our study, BRCA1 mutation carriers with triple-negative disease had a higher histologic grade (grade 3, 87%) than non-triple-negative BRCA1 mutation carriers (grade 3, 38.9%). The ratio of non-triple-negative BRCA1 mutation carriers with a higher histologic grade was lower (38.9%) in our study than in the aforementioned study that evaluated the nuclear grade status (75%) in these patients (5).

This study has some limitations. First, this had a retrospective design, which may have restricted the retrieval of the data from patient archives. Second, it was conducted in two tertiary care centers in İstanbul. However, no studies have investigated Turkish patients with breast cancer and focused on the clinical and pathological characteristics of these patients based on their BRCA mutation profiles. Therefore, to the best of our knowledge, this study is the first to report this issue that represents the Turkish population in a large series of patients with high-risk breast cancer.

In conclusion, in this study, more patients with BRCA1-related breast cancers had triple-negative disease, poorly differentiated with a high histologic grade, and a higher ratio of lymphovascular invasion than patients with BRCA-negative and BRCA2-related breast cancers. In our clinical practice, all these findings, which are usually associated with a poor prognosis, support that BRCA1-related breast cancers represent a distinct group of patients with unique clinical and pathological features from other patients with breast cancer.

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of İstanbul Professor Doctor Cemil Taşçıoğlu City Hospital (approval no: 48670771-514.10/210).

Informed Consent: Retrospective study.

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Authorship Contributions

Conception: M.M.A., Ç.G., Ş.S., N.Y., A.S., Se.A., M.G.; Design: M.M.A., Ç.G., Ş.S., S.A., R.Ç., O.C., Ş.C., A.S., Se.A., M.G.; Supervision: Ç.G., S.A., R.Ç., N.Y., O.C., Ş.C., A.S., Se.A., M.G.; Materials: B.E., N.Y., O.C., Se.A., M.G.; Data Collection or Processing: M.M.A., B.E., Ş.C., S.A., R.Ç., N.Y., O.C., Ş.C., Se.A., M.G.; Analysis or Interpretation: M.M.A., Ç.G., B.E., S.A., R.Ç., N.Y., O.C., Ş.C., A.S., Se.A., M.G.; Literature Search: M.M.A., S.A., R.Ç., A.S; Writing: M.M.A., Ç.G., Ş.S., N.Y., O.C., Ş.C., A.S; Critical Review: M.M.A., Ç.G., Ş.S., S.A., R.Ç., N.Y., O.C., Ş.C., A.S., Se.A., M.G.

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Original Article

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Clinicopathological Features of Breast Cancer with Polysomy 17 and Its Response to Neoadjuvant Chemotherapy

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ABSTRACT

Objective: The interpretation of human epidermal growth factor receptor 2 *(HER2)* fluorescence *in situ* hybridization (FISH) results may be challenging in tumors with polysomy 17, which is defined as increased signals of chromosome enumeration probe 17 (CEP17). The effect of polysomy 17 on *HER2* protein expression and tumor treatment response has not been established. In this retrospective study, we investigated the clinicopathological features of breast cancer with polysomy 17 and determined the tumors' response to neoadjuvant chemotherapy (NACT).

Materials and Methods: The study included 366 patients with primary breast cancer whose tumors had a CEP17 count of ≥ three/nucleus based on *HER2* FISH studies. These cases were categorized according to *HER2*/CEP17 ratio and *HER2* signals/nucleus using the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. We compared the clinicopathological characteristics and tumor response to NACT among different groups.

Results: There was a statistically significant difference in patients' age at diagnosis, tumor pathological grade, estrogen and progesterone receptor status, and NACT response among different *HER2* FISH groups. Polysomy 17 tumors in group 1 had a higher rate of response (pathological complete response and residual cancer burden class I) to NACT containing anti-*HER2* reagent than did those in other groups (p = 0.004), whereas polysomy 17 tumors in group 3 did not show a significant response to anti-*HER2* treatment.

Conclusion: Polysomy 17 tumors in different *HER2* FISH groups have different pathological features and respond to NACT differently. These results may help us identify patients who will benefit from anti-*HER2* therapy.

Keywords: Polysomy 17, breast cancer, *HER2* FISH study, neoadjuvant chemotherapy

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Key Points

- Polysomy 17 tumors show different clinicopathological characteristics among different *HER2* FISH groups.
- Polysomy 17 tumors show a different response to NACT among different *HER2* FISH groups.
- Polysomy 17 tumors in group 3 did not show a significant response to anti-*HER2* treatment.

Introduction

Human epidermal growth factor receptor 2 (HER2) is a member of the human epidermal growth factor receptor family, encoded by the gene *HER2* on 17q12-21.32 (1). Around 20% of invasive breast cancer cases overexpress or exhibit amplification of *HER2* (HER2+ breast cancer). HER2+ breast cancer is known to be an aggressive disease, with a poor clinical outcome (2). Trastuzumab, a monoclonal antibody that targets HER2, has demonstrated efficacy against HER2+ primary and metastatic breast cancer, both as a single agent and combined with chemotherapy (3, 4). Treatments that include anti-HER2 reagent have become the standard of care for patients with early or advanced HER2+ breast cancer (5, 6).

Accurate detection of HER2 overexpression or gene amplification is crucial in determining patients' eligibility for anti-HER2 treatment and predicting disease prognosis. According to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, HER2 testing is performed using immunohistochemical (IHC) assessment of HER2 protein overexpression and *in situ* hybridization

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(ISH) analysis of *HER2* gene amplification (7). ISH is conducted using either a single probe to enumerate HER2 copies per nucleus only or a dual-probe technique in which the *HER2*/CEP17 ratio is determined via hybridization to the chromosome 17 centromere region using chromosome enumeration probe 17 (CEP17). Although ASCO/CAP provides clear guidance on HER2 assessment, the test results can be difficult to interpret for various reasons, including copy number alterations in different foci on chromosome 17.

Chromosome 17 polysomy is associated with equivocal HER2 results. True polysomy is defined as the presence of extra copies of one or a whole chromosome. However, according to recent studies, true chromosome 17 polysomy is very rare in breast cancer. Focal amplifications encompassing the centromere are a common cause of the increase in CEP17 signals in ISH testing (8). Currently, the commonly adopted threshold for polysomy 17 is a mean of ≥3 CEP17 signals per nucleus (9). Increased CEP17 copies can alter the *HER2*/CEP17 ratio and subsequently influence the interpretation of the final HER2 ISH result. Consequently, 2013 ASCO/CAP recommends the use of a reflex test with alternative chromosome 17 probes for resolving equivocal HER2 ISH results (7).

HER2 FISH testing using alternative chromosome 17 probes can be performed by testing for additional genes on chromosome 17 that are not expected to coamplify with HER2. The commonly used commercially available probes include *SMS* (Smith-Magenis syndrome, also called *RAI1*), *RARA* (retinoic acid receptor alpha), and *TP53* (8). On using these different chromosome 17 genes, *HER2* gene status has been reported to be upgraded from equivocal to amplified or positive in a significant percentage of cases (8, 10, 11). However, in these studies, there were no clinical outcome data available in these patients with "revised" HER2+ breast cancer. The benefit of HER2-targeted therapy in these patient populations was also unknown. A recent study by Sneige et al. (12) demonstrated that the "revised" HER2 status due to the use of alternative chromosome 17 probes was unreflective of patient outcome. They concluded that these alternative chromosome 17 genes might overestimate the number of HER2-positive cases and lead to an erroneous upgrade of HER2 status to "positive."

A better understanding of the biological features of polysomy 17 breast cancer and how polysomy 17 affects *HER2* gene copy number and protein expression could help select patients who will respond to anti-HER2 treatment. In this study, we determined the clinicopathological characteristics of patients with breast cancer with polysomy 17. We also investigated the tumors' response to neoadjuvant chemotherapy (NACT), with and without anti-HER2 reagent.

Materials and Methods

Patient cohort

This retrospective study was conducted in a cohort of 366 patients with primary invasive breast cancer. Tumor HER2 FISH testing was performed at our institution between April 1st, 2013, and March 31st, 2018, and a CEP count ≥3/nucleus was required. Patients with a prior history of breast cancer, those diagnosed with de novo stage IV disease, and those who had multiple HER2 FISH tests using the same specimen were excluded from the study.

We reviewed patients' medical charts to determine clinical variables, including age at diagnosis, tumor pathological characteristics (tumor size, lymph node status, pathological staging, and histological grade), tumor biomarker features [estrogen receptor (ER), progesterone receptor (PR), Ki-67 value, and HER2 immunohistochemical (IHC) analysis], and treatment (with or without NACT and with or without anti-HER2 reagent in the NACT regimen). In patients who received NACT, tumor response to NACT was evaluated according to the pathological residual cancer burden (RCB) (13). A pathological complete response (pCR) and RCB class I were interpreted as a good response, while RCB classes II and III were interpreted as a poor response. Approval was obtained from the Institutional Review Board at our institution (no: PA18-0021) before the initiation of this study.

Immunohistochemical analysis

The IHC analysis performed at our department was processed using formalin-fixed, paraffin-embedded tumor sections (4 μm) with ER Clone 6F11 (Leica Biosystems, Inc., Buffalo Grove, IL) and PR Clone PgR 1294 (Agilent DAKO, Santa Clara, CA). The HER2 IHC analysis was performed using antibody clone AB8 (NeoMarkers) from April 1st, 2013 until August 31st, 2016, and clone 4B5 (Ventana Medical Systems, Inc., Tucson, AZ) from September 1st, 2016, to March 31st, 2018, due to institutional antibody change. The IHC studies (ER, PR, and HER2) conducted at outside institutions were reviewed at our department. ER, PR, and HER2 IHC statuses were interpreted according to the ASCO/CAP guidelines (7, 14).

FISH analysis

HER2 FISH analysis was performed using the Vysis PathVysion probe kit, which includes a SpectrumGreen-conjugated probe for the alpha satellite DNA located at the centromeric region of chromosome 17 (17p11.1-q11.1) and SpectrumOrange-conjugated probe for the *HER2* gene locus (Abbott Molecular/Abbott Laboratories, Abbott Park, IL). The same specimen blocks used for the HER2 IHC study were selected for the FISH study. *HER2* and CEP17 signals in 60 representative invasive cell nuclei were examined. *HER2* FISH result was interpreted according to the ASCO/CAP guidelines (7). For cases that were interpreted as equivocal for *HER2* amplification, another 60 representative invasive cell nuclei were examined.

Polysomy 17 tumors are classified into four *HER2* FISH groups according to the *HER2*/CEP17 ratio and *HER2* signals/nucleus, on the basis of ASCO/CAP guidelines: group 1 had a *HER2*/CEP17 ratio ≥2.0 and *HER2* signals/nucleus ≥4.0; group 3 had a *HER2*/CEP17 ratio <2.0 and *HER2* signals/nucleus ≥6.0; group 4 had a *HER2*/CEP17 ratio <2.0 and *HER2* signals/nucleus ≥4.0 and <6.0; group 5 had a *HER2*/CEP17 ratio <2.0 and *HER2* signals/nucleus <4.0 (15).

Statistical analysis

Categorical variables were summarized using frequencies and percentages. For most categorical clinical and pathological features, group differences were assessed using chi-square and Fisher's exact test. The correlation between the age at diagnosis and tumor *HER2* FISH group was examined by ANOVA analysis. A p-value <0.05 (two-sided) was considered statistically significant.

Results

Group distribution of polysomy 17 tumors

Among the 366 primary invasive breast cancer tumors included in this study, 128 (35.0%) were classified as *HER2* FISH group 1, 21

(5.7%) as group 3, 69 (18.9%) as group 4, and 148 (40.4%) as group 5. Representative *HER2* FISH images of polysomy 17 tumors in each group are shown (Figure 1).

Clinicopathological characteristics of polysomy 17 tumors

The clinicopathological characteristics of invasive breast cancer with polysomy 17 are shown in Table 1. In our study cohort, the mean age of patients at diagnosis was 56 years (range: 24–92 years). Most tumors were of a ductal type [340 of 366 (92.9%)] and histological grade 2 [151 of 365 (41.4%)] or [201 of 365 (55.1%)] with ER expression in over two-thirds of the patients [260 of 366 (71.0%)] and PR expression in half of the patients [184 of 365 (50.4%)].

We investigated the clinicopathological characteristics of polysomy 17 tumors in 4 *HER2* FISH groups. The histological types did not differ significantly; however, there were statistically significant differences in the age of the patients at diagnosis, tumor nuclear and histological grade, and ER/PR status. Patients with group 1 polysomy 17 tumors were diagnosed at a slightly younger age (mean age: 54 years) than were those with groups 4 (mean age: 57 years) and 5 (mean age: 58 years) tumors ($p<0.05$). Histological grade 3 tumors were more frequently observed in group 1 [81 of 127 (63.8%)] than in groups 3 [6 of 21 (28.6%)] and 5 [73 of 148 (49.3%)] ($p<0.05$). ER negative tumors were more common in group 1 [52 of 128 (40.6%)] than in groups 4 [14 of 69 (20.3%)] and 5 [35 of 148 (23.6%)] ($p<0.05$). PR negative tumors were more common in group 1 [86 of 128 (67.2%)] than in the other three groups [5 of 21 (23.8%) in group 3; 26 of 69 (37.7%) in group 4; 64 of 147 (43.5%) in group 5] ($p<0.001$).

Next, we evaluated tumor size and axillary lymph node status in 185 polysomy 17 tumors without NACT treatment (Table 2). These tumors were predominantly low stage [109 (58.9%) were pT1 and 63 (34.1%) were pT2], and only 13 (7%) were pT3 or pT4. No differences were observed in tumor pathological staging among the four groups. One-third of the tumors [52 of 185 (30.2%)] had metastasized to the axillary lymph nodes at the time of surgery. Tumors in group 1 had a significantly lower metastatic rate than did tumors in group 5 (16.7% vs 37.0%, $p<0.05$).

Comparison of IHC and FISH for HER2 status in polysomy 17 tumors

The HER2 IHC and FISH test results of the 366 tumors are outlined in Table 3: 92 tumors (26.3%) were positive (score 3+) on HER2 IHC testing, 145 (41.4%) were equivocal (score 2+), and 113 (32.3%) were negative, with a score of 1+ [92 of 113 (81.4%)] or 0 [21 of 113 (18.6)].

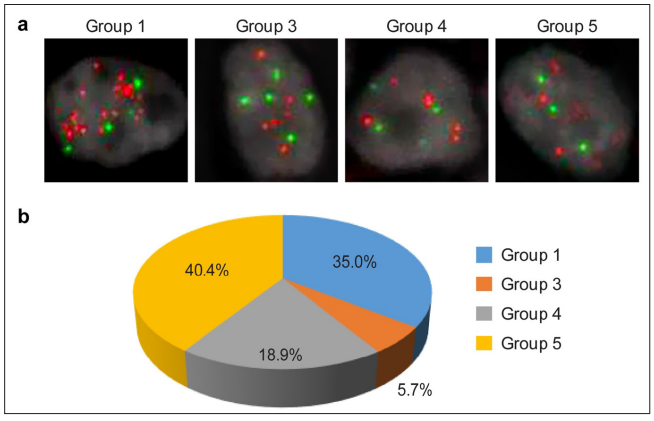

Figure 1. Representative *HER2* FISH images of polysomy 17 tumors in different *HER2* FISH groups (a); proportions of each group (b)

HER2: Human epidermal growth factor receptor 2; FISH: Fluorescence in situ hybridization

The distribution of HER2 IHC results was significantly different among tumors in the four *HER2* FISH groups ($p<0.001$). In group 1, most tumors [86 of 123 (69.9%)] were positive (score 3+) on HER2 IHC testing, about a quarter [34 of 123 (27.6%)] were equivocal (score 2+), and only a small number [3 of 123 (2.5%)] were negative (score 1+). No tumors had a HER2 IHC score of 0 in this group.

In contrast, most tumors [75 of 138 (54.4%)] in group 5 were negative for HER2 IHC staining, with a score of 1+ [60 of 138 (43.5%)] or 0 [15 of 138 (10.9%)]. Fewer tumors in this group [62 of 138 (44.9%)] were equivocal (score 2+), and only one tumor (0.7%) was positive (score 3+). In group 3, five tumors (23.8%) were positive (score 3+) on HER2 IHC testing; this was significantly lower than the number of tumors in group 1 ($p<0.001$) but higher than that in groups 4 ($p<0.05$) and 5 ($p<0.001$).

NACT response in polysomy 17 tumors

In our study cohort, 181 patients underwent NACT after initial diagnosis. Of these, 97 patients received an anti-HER2 therapy, and 84 did not. RCB was calculated for 175 tumors to evaluate the response to NACT (13). RCB could not be calculated for six tumors because of insufficient parameters of residual cancer in the breast or lymph nodes after NACT (all cases were from outside facilities). As shown in Table 4, 82 of 175 patients (46.9%) experienced a good response, while 93 (53.1%) had a poor response to NACT.

Tumors in different *HER2* FISH groups had different responses to NACT ($p<0.001$). Overall, a significant number group 1 tumors had a good response compared with tumors in other groups: 56 tumors (70.9%) in group 1 had a pCR or RCB I compared with three tumors (30.0%) in group 3 ($p<0.05$), eight (30.8%) in group 4 ($p<0.001$), and 15 (25%) in group 5 ($p<0.001$). Most patients with group 1 or 3 tumors received an anti-HER2 reagent containing NACT. Of these, 55 tumors (72.4%) in group 1 had a good response compared with three of nine in group 3 (33.3%) ($p<0.004$). In contrast, most patients with group 4 or 5 tumors did not receive an anti-HER2 reagent; 33.3% and 26.8% of these tumors had a good response, respectively.

We also investigated the pathological features associated with tumor response to NACT, with or without anti-HER2 therapy. *HER2* FISH group 1, ER negativity, PR negativity, and HER2 overexpression were associated with a good response to treatment with anti-HER2 reagent (Table 5). A high nuclear and histological grade, ER negativity, PR negativity, and high proliferative index Ki-67 were associated with a good response to treatment without anti-HER2 reagent (Table 6).

Discussion and Conclusion

Polysomy has been proposed to explain the increased rates of *HER2* amplification or discordance between IHC and FISH results. The results of recent studies have suggested that, detected by FISH, the major contributor to polysomy 17 is a significantly increased copy number of CEP17 secondary to the amplification of larger segments of chromosome 17, involving both *HER2* and the centromere (8). An elevated CEP17 count is frequently observed in invasive breast cancer. Using the cut-off of ≥3 CEP17 copies per cell, reported prevalence

rates of polysomy 17 tumors have ranged from 3% to 46% across various studies (16-23).

Polysomy 17 contributes to increased *HER2* FISH equivocal results. To resolve this problem, the 2013 ASCO/CAP guidelines advocate additional testing in these cases. Many studies have tested for additional genes on chromosome 17 and have upgraded a significant portion of equivocal cases to *HER2* amplified or positive (10-12). However, recent studies have demonstrated the presence of frequent complex structural alterations of chromosome 17 in patients with breast cancer, with losses and gains of genetic material at different loci of the chromosome (10, 24). As a consequence, the use of additional FISH probes is not sufficient for correcting the *HER2* gene status. Currently, there is no standard method to detect the *HER2* gene status in polysomy 17 breast cancer.

The reported clinicopathological features of polysomy 17 tumors are controversial. Several studies have linked polysomy with unfavorable pathological features, such as high proliferative activity, high Nottingham Prognostic Index Score, and nodal involvement (19, 23, 25), while other studies have found no significant differences between polysomic and nonpolysomic primary breast cancer in terms of clinicopathological variables and patient survival (18, 21). In our study cohort, most of the polysomy 17 tumors are histological grade

Table 1. Clinical and pathological characteristics of patients with primary breast cancer with polysomy 17 tumors

Characteristic	Total (n = 366)	Group 1 (n = 128)	Group 3 (n = 21)	Group 4 (n = 69)	Group 5 (n = 148)	p-value
Age, years						
Mean	56	54	55	57	58	
Range	24–92	24–90	34–75	32–92	24–85	**0.044⁺**
				*	*	
Histological type, n (%)						
IDC, NOS	340 (92.9)	122 (95.3)	20 (95.2)	65 (94.2)	133 (89.9)	
ILC	9 (2.5)	2 (1.6)	1 (4.8)	1 (1.4)	5 (3.4)	0.701⁺⁺
Other	17 (4.6)	4 (3.1)	0 (0)	3 (4.4)	10 (6.7)	
Nuclear grade, n (%)						
I	2 (0.5)	1 (0.7)	0 (0)	0 (0)	1 (0.7)	
II	151 (41.3)	39 (30.5)	15 (71.4)	27 (39.1)	70 (47.3)	**0.004⁺⁺**
III	213 (58.2)	88 (68.8)	6 (28.6)	42 (60.9)	77 (52)	
			**		*	
Histological grade, n (%)						
1	13 (3.5)	2 (1.6)	1 (4.7)	3 (4.4)	7 (4.8)	
2	151 (41.4)	44 (34.6)	14 (66.7)	25 (36.2)	68 (45.9)	
3	201 (55.1)	81 (63.8)	6 (28.6)	41 (59.4)	73 (49.3)	**0.04⁺⁺**
NA	1	1	0	0	0	
			*		*	
ER, n (%)						
Positive	260 (71.0)	76 (59.4)	16 (76.2)	55 (79.7)	113 (76.4)	
Negative	106 (29.0)	52 (40.6)	5 (23.8)	14 (20.3)	35 (23.6)	**0.005⁺⁺**
				*	*	
PR, n (%)						
Positive	184 (50.4)	42 (32.8)	16 (76.2)	43 (62.3)	83 (56.5)	
Negative	181 (49.6)	86 (67.2)	5 (23.8)	26 (37.7)	64 (43.5)	
NA	1	0	0	0	1	**<0.001⁺⁺**
			**	**	**	

Important p-values shown in bold.

*p<0.05 compared with group 1; **p<0.001 compared with group 1; ⁺: one-way ANOVA analysis; ⁺⁺: Chi-square analysis; IDC: Invasive ductal carcinoma; NOS: Invasive ductal carcinoma of no specific type; ILC: Invasive lobular carcinoma; ER: Estrogen receptor; PR: Progesterone receptor; NA: Not available; n: Number

2 or 3. ER positivity was seen in 71.4% of tumors, which is a slightly lower rate than the known 75%–80% rate in invasive breast cancer (Table 1). This indicates that polysomy 17 tumors display unfavorable pathological features.

In addition, polysomic *HER2*-amplified tumors have been reported to have more unfavorable pathological features than polysomic *HER2*-nonamplified tumors (20). Since *HER2* FISH group 1 tumors are HER2 amplified and *HER2* FISH group 5 tumors are HER2 nonamplified, we compared the clinicopathological features of the tumors in these two groups. Group 1 tumors were more likely to be diagnosed in younger patients ($p<0.01$), have a higher histological grade ($p<0.05$), and be ER negative ($p<0.01$) and PR negative ($p<0.001$) than were group 5 tumors (Table 1). These findings agree with previous findings that HER2-positive breast cancer is more likely to be diagnosed in younger patients and be more aggressive (2). However, when the tumor stage and axillary lymph node status in these two groups were compared, group 1 tumors were found to have a lower lymph node metastatic rate ($p<0.05$). No significant difference was observed in tumor stage between these two groups (Table 2). The reason why polysomic *HER2*-amplified tumors had a lower risk of lymph node metastasis needs to be further studied.

The effect of polysomy 17 on HER2 alteration also needs to be further investigated. Some studies have shown that polysomy 17 alone might not significantly contribute to the variation in *HER2* copy number and HER2 protein overexpression (16), while other studies have correlated polysomy 17 with an increased HER2 IHC score in tumors without *HER2* amplification (22, 26-28). For example, Hyun et al. (27) reported a significantly higher incidence of elevated CEP17 count in tumors with HER2 IHC score 2+/3+ compared with tumors with score 0/1+. In addition, Varshney et al. (22) and Petroni et al. (23) found that high CEP17 counts were associated with HER2 IHC score 3+ staining. Our results showed that 67.7% of polysomy 17 tumors were HER2 IHC score 2+/3+, and 32.3% of tumors were score 0/1+. In group 5, 44.9% of tumors were HER2 IHC score 2+, and one tumor (0.7%) was score 3+ (Table 3). This percentage was dramatically higher than that reported by the BCIRG clinical trial, in which 0.55% of group 5 tumors (including polysomy 17 and non-polysomy 17 tumors) had a HER2 IHC score 2+/3+ (14). Although this difference could be due to variations in the population under study

Table 2. Pathological stage of polysomy 17 tumors that had not received NACT

	Total	Group 1	Group 3	Group 4	Group 5	
Stage	**(n = 185)**	**(n = 46)**	**(n = 11)**	**(n = 42)**	**(n = 86)**	**p-value**
Tumor stage, n (%)						
pT1	109 (58.9)	30 (65.2)	6 (54.5)	24 (57.1)	49 (57)	
pT2	63 (34.1)	15 (32.6)	4 (36.4)	16 (38.1)	28 (32.6)	0.665
pT3 + T4	13 (7.0)	1 (2.2)	1 (9.1)	2 (4.8)	9 (10.4)	
Lymph node stage, n (%)						
pN0	120 (69.8)	35 (83.3)	7 (77.8)	27 (67.5)	51 (63)	
pN1 + N2 + N3	52 (30.2)	7 (16.7)	2 (22.2)	13 (32.5)	30 (37.0)	0.121
NA	13	4	2	2	5	
					*	

*p<0.05 compared with group 1.
NACT: Neoadjuvant chemotherapy; NA: Not available; n: Number

Table 3. HER2 protein expression in polysomy 17 tumors

	Total	Group 1	Group 3	Group 4	Group 5	
	(n = 366)	**(n = 128)**	**(n = 21)**	**(n = 69)**	**(n = 148)**	**p-value**
HER2 IHC score, n (%)						
0	21 (6.0)	0 (0)	2 (9.6)	4 (5.8)	15 (10.9)	
1+	92 (26.3)	3 (2.5)	7 (33.3)	22 (32.4)	60 (43.5)	
2+	145 (41.4)	34 (27.6)	7 (33.3)	42 (61.8)	62 (44.9)	**<0.001**
3+	92 (26.3)	86 (69.9)	5 (23.8)	0 (0)	1 (0.7)	
NA	16	5	0	1	10	
			**	**	**	

**p<0.001 compared with group 1. Important p-values are shown in bold.
HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemical; NA: Not available; n: Number

Table 4. Treatment response of polysomy 17 tumors in HER2 FISH group to NACT

	Total	Group 1	Group 3	Group 4	Group 5	
Treatment	**(n = 181)**	**(n = 82)**	**(n = 10)**	**(n = 27)**	**(n = 62)**	**p-value**
NACT overall, n (%)						
pCR + RCB I	82 (46.9)	56 (70.9)	3 (30)	8 (30.8)	15 (25)	
RCB II + III	93 (53.1)	23 (29.1)	7 (70)	18 (69.2)	45 (75)	**<0.001**
NA	6	3	0	1	2	
			*	**	**	
NACT with anti-HER2, n (%)						
pCR + RCB I	59 (62.8)	55 (72.4)	3 (33.3)	1 (20)	0 (0)	
RCB II + III	35 (37.2)	21 (27.6)	6 (66.7)	4 (80)	4 (100)	**0.004**
NA	3	2	0	1	0	
			*	*	*	
NACT without anti-HER2, n (%)						
pCR + RCB I	23 (28.4)	1 (33.3)	0 (0)	7 (33.3)	15 (26.8)	
RCB II + III	58 (71.6)	2 (66.7)	1 (100)	14 (66.7)	41 (73.2)	0.856
NA	3	1	0	0	2	

Important p-values are shown in bold.

*p<0.05 compared with group 1; **p<0.001 compared with group 1; NACT: Neoadjuvant chemotherapy; FISH: Fluorescence *in situ* hybridization; NA: Not available; RCB: Residual cancer burden; n: Number; HER2: Human epidermal growth factor receptor 2

and test methods, the high percentage of tumors with HER2 IHC score 2+/3+ in our patients with *HER2*-nonamplified tumors indicates that polysomy 17 is associated with an increased HER2 IHC score.

The potential association between polysomy 17 and HER2 expression raises the question of whether polysomy 17 influences anti-HER2 treatment response. Some data indicate that polysomy 17 tumors are sensitive to anti-HER2 treatment. In a study by Hofmann et al. (17), two patients with HER2 overexpression (IHC 3+) due to polysomy rather than HER2 amplification experienced a response to trastuzumab. In contrast, phase III EGF30001 trial revealed that lapatinib had no significant benefit in patients with *HER2*-nonamplifed, polysomic metastatic breast cancer (29). We evaluated the response of polysomy 17 tumors to NACT in the presence or absence of anti-HER2 reagent. Our results indicated that patients with *HER2* FISH group 1 tumors who received NACT containing an anti-HER2 reagent had a higher good response rate than did patients with other groups of tumors who received NACT, with or without anti-HER2 reagent. In group 5 tumors, one patient had a tumor that showed HER2 overexpression (IHC score 3+). However, this patient did not undergo NACT. In reviewing the pathological features associated with tumor response to NACT, our results revealed that, for tumors treated with NACT containing an anti-HER2 reagent, the *HER2* FISH group, ER and PR status, and HER2 expression level were associated with treatment response. For tumors treated without anti-HER2 reagent, tumor nuclear and histological grade, proliferative index Ki-67, and ER and PR status were correlated with response.

Another finding was that, in our study cohort, *HER2* FISH group 3 tumors, which were designated as *HER2*-amplified tumors according to 2013 ASCO/CAP guidelines, did not demonstrate a significant response to NACT containing anti-HER2 reagent. This finding supports the recently published update to the ASCO/CAP guidelines that HER2 status in group 3 tumors should be interpreted combined with the FISH result and HER2 protein expression level (30). To our knowledge, this is the first report of the treatment response of polysomy 17 tumors in the NACT setting. Further study in a larger population is needed to confirm these findings.

In summary, we studied the clinicopathological features and tumor response to NACT treatment of polysomy 17 breast cancer on the basis of tumor *HER2* FISH groups. We conclusively demonstrated that group 1 polysomy 17 tumors have more unfavorable pathological features but have the best response to NACT with anti-HER2 treatment. Polysomy 17 tumors in other groups did not significantly benefit from anti-HER2 treatment in the NACT setting. These results could help identify patients who may benefit from a more intensive targeted therapy regimen.

Table 5. Pathological features associated with response to NACT with anti-HER2 reagent in polysomy 17 tumors

	pCR + RCB I	RCB II + RCB III	
Feature	**(n = 59)**	**(n = 35)**	**p-value**
HER2 FISH group, n (%)			
1	55 (93.2)	21 (60.0)	**-**
3	3 (5.1)	6 (17.1)	**0.02**
4	1 (1.7)	4 (11.4)	**0.02**
5	0 (0)	4 (11.4)	**0.008**
HER2 IHC score, n (%)			
0	0 (0)	2 (5.7)	
1+	1 (1.8)	6 (17.1)	
2+	15 (26.8)	10 (28.6)	**<0.05**
3+	40 (71.4)	17 (48.6)	
NA	3	0	
ER, n (%)			
Positive	28 (47.5)	26 (74.3)	**<0.05**
Negative	31 (52.5)	9 (25.7)	
PR, n (%)			
Positive	13 (22.0)	19 (54.3)	**<0.05**
Negative	46 (78.0)	16 (45.7)	
Ki-67, n (%)			
<15	5 (9.8)	1 (4.5)	
15–<35	15 (29.4)	7 (31.8)	0.821
≥35	31 (60.8)	14 (63.6)	
NA	8	13	
Nuclear grade, n (%)			
II	18 (30.5)	15 (42.9)	0.225
III	41 (69.5)	20 (57.1)	
Histological grade, n (%)			
1	1 (1.7)	0 (0)	
2	19 (32.2)	19 (54.3)	0.063
3	39 (66.1)	16 (45.7)	

Important p-values are shown in bold.

NACT: Neoadjuvant chemotherapy; HER2: Human epidermal growth factor receptor 2; FISH: Fluorescence *in situ* hybridization; IHC: Immunohistochemical; RCB: Residual cancer burden; NA: Not available. ER: estrogen receptor; PR: progesterone receptor; n: Number

Table 6. Pathological features associated with response to NACT without anti-HER2 reagent in polysomy 17 tumors

	pCR + RCB I	RCB II + RCB III	
Feature	**(n = 23)**	**(n = 58)**	**p-value**
Nuclear grade, n (%)			
II	2 (8.7)	28 (48.3)	**<0.001**
III	21 (91.3)	30 (51.7)	
Histological grade, n (%)			
1	0 (0)	1 (1.7)	
2	2 (8.7)	29 (50.0)	**<0.001**
3	21 (91.3)	28 (48.3)	
ER, n (%)			
Positive	8 (34.8)	39 (67.2)	**<0.05**
Negative	15 (65.2)	19 (32.8)	
PR, n (%)			
Positive	3 (13.0)	27 (46.6)	**<0.05**
Negative	20 (87)	31 (53.4)	
Her2 IHC score, n (%)			
0	4 (19)	5 (9.4)	
1+	9 (42.9)	25 (47.2)	0.521
2+	8 (38.1)	23 (43.4)	
NA	2	5	
HER2 FISH group, n (%)			
1	1 (4.3)	2 (3.4)	
3	0 (0)	1 (1.7)	0.837
4	7 (30.4)	14 (24.1)	
5	15 (65.2)	41 (70.7)	
Ki-67, n (%)			
<15	0 (0)	8 (15.4)	
15–<35	2 (11.8)	24 (46.2)	**<0.05**
≥35	15 (88.2)	20 (38.5)	
NA	6	6	

Important p-values are shown in bold.

NACT: Neoadjuvant chemotherapy; HER2: Human epidermal growth factor receptor 2; FISH: Fluorescence *in situ* hybridization; IHC: Immunohistochemical; RCB: Residual cancer burden; NA: Not available. ER: estrogen receptor; PR: progesterone receptor; n: Number

Ethics Committee Approval: Approval was obtained from the Institutional Review Board at our institution (PA18-0021) before the initiation of this study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: H.S., J.C., H.C., A.A.Ş., G.T., M.R., B.L.; Design: H.S., J.C., H.C., A.A.Ş.; Supervision: A.A.Ş., B.L.; Data Collection or Processing: H.S., H.C., A.A.Ş., G.T.; Analysis or Interpretation: H.S., H.C., A.A.Ş., G.T.; Literature Search: H.S.; Writing: H.S., B.L.; Critical Review: H.C., A.A.Ş., G.T., B.L.

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Original Article

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The Relationship of Mutation Carriage of *BRCA1/2* and Family History in Triple-Negative Breast Cancer: Experience from a Diagnostic Center in Turkey

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ABSTRACT

Objective: *BRCA1/2* genes play a role in the etiopathogenesis of 10%–30% of triple-negative breast cancer (TNBC). This study aims to investigate the *BRCA1/2* genes and the demographic and clinicopathological features in patients with TNBC. The study also examined the impact of cancer history of TNBC individuals' relatives on the risk of *BRCA1/2* mutation carriership rate.

Materials and Methods: The *BRCA1/2* genes of 65 women diagnosed with TNBC between 2011 and 2017 were investigated using next-generation sequencing. We analyzed the correlations of patients' demographic and clinicopathologic parameters and family history with *BRCA1/2* mutation status. We used the χ^2-test, t-test, Mann-Whitney U test, and logistic regression statistical methods.

Results: The *BRCA1/2* mutation carrier rate was 16.9%. Patients who had *BRCA1/2* mutations were compared with those who did not in terms of demographic and clinicopathological parameters. In the *BRCA1/2* mutation carrier group, the Ki-67 index and the number of relatives with cancer were higher than the *BRCA1/2* non-carrier group. Logistic regression analysis revealed that when the number of relatives with breast or ovarian cancer was ≥2, the risk of carrying the *BRCA1/2* mutation increased by 15-fold. Regardless of the type of cancer (including cancers in other organs besides breast or ovary), the risk of carrying the *BRCA1/2* mutation increased 1.3 times with each increase in the number of relatives with cancer for the patient with TNBC.

Conclusion: In cases with a diagnosis of TNBC, a significant relationship exists between the number of relatives with cancer in the family history and the risk of carrying mutations in the *BRCA1/2* genes. This relationship can be confirmed further by large-scale studies with more cases.

Keywords: *BRCA1/2*, family history, hereditary cancer, triple-negative breast cancer

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Key Points

- TNBC type breast cancers are frequently seen in *BRCA1/2* genes mutation carriers.
- The Ki67 index of *BRCA1/2* gene mutation carriers is high in TNBC.
- In TNBC, the family cancer history is important at the risk of *BRCA1/2* carriage.

Introduction

Breast cancer is the most common type of cancer in females worldwide, and it is the most common cause of cancer-related death in females (1). Triple-negative breast cancer (TNBC) constitutes approximately 12%–24% of breast cancers, highly heterogeneous regarding clinical behavior, morphological features, and genetic background (2). The TNBC subtype is more commonly seen in certain ethnic groups (like African-American, and Hispanic), and *BRCA1/2* gene mutation carriers are often diagnosed as intermediate cancer (3). TNBC has a poor prognosis than other breast cancers in terms of relapse rate, frequency of metastasis, and survival parameters. The expression of estrogen receptors (ER) and progesterone receptors (PR) and amplification of *HER2* have not been observed in these cancers in analyzes performed using immunohistochemisty. Therefore, endocrine therapies or anti-*HER2* therapies cannot be used in these patients (4). Genetic causes play an essential role in the etiopathogenesis of TNBC. The best-known genetic risk factors are *BRCA1*/2 mutations, which lead to hereditary breast and ovarian cancer syndrome. These genes are involved in controlling the cell cycle, chromatin remodeling, and epigenetic regulation. Loss of function mutations in these tumor suppressor genes, which are important for the continuation of genomic integrity, contribute to initiating carcinogenesis. The prevalence of carrying *BRCA1*/2 mutations has been reported as 3% in all breast cancer patients and 10%–30% in TNBC patients (5). Approximately 70%

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of breast cancers are observed in *BRCA1* germline mutation carriers, and 16%–23% of breast cancers in *BRCA2* germline mutation carriers are the TNBC subtype (6-7). This single-center cohort study aims to evaluate the relationship between the *BRCA1/2* mutation status and demographic characteristics, clinicopathological details, and family cancer histories of 65 patients diagnosed with TNBC.

Materials and Methods

In this study, 65 Turkish female patients with TNBC from the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Medical Genetics, were investigated between 2011 and 2017 for their breast cancer's genetic etiology. *BRCA1/2* test standards were applied to the patients in accordance with the National Comprehensive Cancer Network Guidelines (8). They were over 18 years old, and their breast cancers were diagnosed as the primary tumor. The patients' family history was evaluated by examining at least three generations of pedigree analyses. This study was conducted by considering ethical responsibilities according to the Declaration of Helsinki and approved by the independent Ethics Committee of the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital approved this study (no: 2020-02/536). In this study, all patients were informed about genetic tests and the use of their information, and their consent was obtained.

All patients' breast cancer was histologically confirmed, and staging was determined based on the sixth edition of the American Joint Committee on Cancer (9). If the percentage of cells stained positive by immunohistochemistry was less than 1%, the ER and PR status was evaluated as negative. For *HER2* gene amplification in IHC staining, membranous staining was graded from 0 to +3. Patients with a staining pattern of +2 were evaluated using the fluorescent *in situ* hybridization method. Those with <2 copies of the *HER2* gene were considered negative.

Patients' genetic analyzes were conducted on the Ion S5™ platform with the next-generation sequencing method and used the Oncomine™ *BRCA* Research Assay kit. In the analysis, all the coding regions of *BRCA1/2* genes and the part containing the 25 base pairs of exon-intron junctions were investigated. The presence of genomic copy number changes in patients was also investigated using a Multiplex ligation-dependent probe amplification method. The Ion Reporter Software Version 5.4 program was used in the bioinformatics analysis of the obtained data. For *BRCA1* and *BRCA2* genetic analysis, the accession numbers used were NM_007294.3 and NM_000059.3, respectively. Sequence variants were classified using algorithms in the American College of Medical Genetics and Genomics guideline (10).

SPSS (IBM SPSS Statistics 24) program was used in the statistical evaluation of all results. In this study, the χ^2-test, t-test, Mann-Whitney U test and logistic regression analysis were used, and $p<0.05$ was considered statistically significant.

Results

The mean age of diagnosis of 65 patients included in this study was 41±10 years. Most patient (73.9%) visits were due to a palpable mass when a cancer diagnosis was made. Of these patients, TNBC was grade 3 in 50%, invasive ductal carcinoma in 80%, and approximately 1-3 cm mass in 72%. The demographic and clinicopathological characteristics of these 65 patients are presented in Table 1. Women who smoked at least ten cigarettes a day for more than ten years were considered positive. In the oral contraceptive usage parameter, patients' use for five years and longer was positive. Among the relatives of patients in the study group, 20 different types of cancer were detected, including breast, ovarian, endometrium, colon, stomach, liver, biliary tract, lung, laryngeal, bladder, kidney, brain, leukemia, lymphoma, oral, skin, and thyroid cancers. The most common cancers among the relatives were breast, lung, colon, stomach, larynx, prostate, and uterus cancers (Figure 1). In the grouping of relatives diagnosed with cancer, the number of relatives diagnosed with breast and ovarian cancer and the relatives who were diagnosed with any cancer, regardless of the cancer type was determined from pedigree analysis. In our study, the total prevalence of *BRCA1*/2 mutations evaluated was 16.9% (11/65). Of *BRCA1*/2 mutations, 63.6% were in *BRCA1* (7/11), and 36.4% were in *BRCA2* (4/11). The majority of *BRCA1* mutations were of the nonsense type, whereas all *BRCA2* mutations were of the frameshift type. All mutations were detected in the heterozygous state. Two of these mutations have not been reported before (Table 2). Patients with and without *BRCA1*/2 pathogenic variants were compared statistically regarding demographic and clinicopathological features (Table 3). In the group with the *BRCA1*/2 mutation, the Ki-67 index and the number of relatives with cancer were higher than *BRCA1*/2 mutation-negative group. When other parameters were investigated, no statistically significant difference was found between the groups. The mean Ki-67 index of all patients in the study was 53 (range: 5–100). This Ki-67 index was 78 in the *BRCA1*/2 mutation carrier group and 40 in *BRCA1*/2 mutation-negative group. The difference between these two groups was statistically significant ($p = 0.022$) (Table 4). Logistic regression analysis was performed to investigate the association of *BRCA1*/2 mutation carrier status and the number of relatives with breast and ovarian cancer. There was a significant relationship between the number of relatives with cancer and *BRCA1*/2 mutation carrier status ($p = 0.006$). Those who have two or more relatives with cancer had a 15 times higher risk of carrying a disease-related variant in *BRCA1/2* than those without cancer relatives (Table 5). A logistic regression analysis was also performed to investigate the relationship between *BRCA1*/2 mutation status and all relatives with cancer regardless of the cancer type. In this model, a significant correlation was found ($p = 0.047$). The risk of *BRCA1*/2 mutation carrier status means 1.3 times increased risk for cancer among the relatives (Table 6).

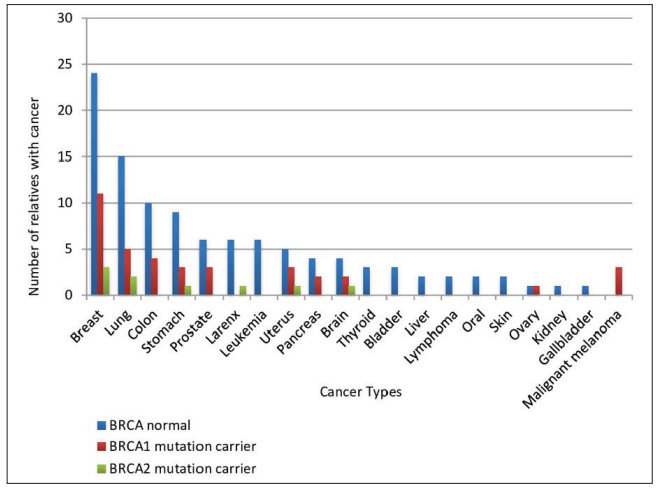

Figure 1. Types of cancer in relatives and the distribution percentages between those with and without *BRCA* mutations

BRCA: Breast cancer susceptibility genes

Table 1. Baseline patient demographics and clinicopathological details

Characteristics (n = 65)		n	%
Age	≤40	23	35
X ± SD → 45.09±10.38, (years)	>40	42	65
Age at diagnosis	≤40	34	52
X ± SD → 40.86±10.28, (years)	>40	31	48
***BRCA1/2* mutation status**	Non-carriers	54	83
	Carriers	11	17
Residence	Rural	11	17
	City	54	83
Level of education	Elementary school	27	42
	High school	22	33
	University	16	25
Working status	No	41	63
	Yes	24	37
Marital status	Single	7	11
	Married	58	89
Number of children	No	11	17
	Up to 4	50	77
	≥4	4	6
Smoking	No	51	79
	Yes	14	21
Oral contraceptive use (years)	No	54	83
	1–5	7	11
	≥5	4	6
Chronic disease	No	44	68
	Yes	21	32
Menopause status	Premenopause	40	62
	Postmenopause	25	38
Family history of all types of cancers	No	16	25
	≤2	27	42
	≥3	22	33
Family history of breast/ovarian Ca	Breast	25	38
	Ovarian	20	31
Tumor localization	Right	34	52
	Left	30	46
	Bilateral	arr1	2
The first symptome of Ca	Palpable mass (right)	23	35
	Palpable mass (left)	25	39
	Swelling, disfigurements, nipple discharge (right)	2	8
	Swelling, disfigurements, nipple discharge (left)	5	6
	Routine check	8	12
Tumor size (cm)	≤2	28	43
	>2	36	55
	Multifocal	1	2

Table 1. Continued

Characteristics (n = 65)		n	%
Tumor size (cm)	≤2	28	43
	>2	36	55
Histopathology	Multifocal	1	2
	Invasive ductal carcinoma	52	80
	Musinoz carcinoma	2	3
	Metaplastic carcinoma	3	5
	Medullary carcinoma	4	6
	Apocrine carcinoma	1	2
	Invasive lobular carcinoma	1	2
	Others	2	4
Tumor grade	1	2	3
	2	13	20
	3	50	77
Ki-67	>60	22	34
	41–60	7	11
	21–40	19	29
	≤20	9	14
	No available data	8	12
Metastases at the diagnosis	No	41	63
	Lymph node	22	34
	Distant sites (lung, brain)	2	3

Ca: Cancer; SD: Standard deviation; n: Number; BRCA: Breast cancer susceptibility genes

Discussion and Conclusion

TNBC is a breast cancer subtype with clinically aggressive behavior and poor prognosis with limited treatment options and poor overall and disease-free survival. This cancer type is extremely heterogeneous regarding clinical, genetic, and histopathologic features. In this cohort study, the mutation status *BRCA1*/2 and general demographic and clinicopathological features of 65 Turkish women diagnosed with TNBC were investigated to elucidate TNBC's complex nature. In this study, TNBC's features were compatible and concordant with the literature regarding parameters such as high Ki-67 index values, diagnosis at an early age and premenopausal period, and mutation status of *BRCA1/2* (1-7). In the literature, the *BRCA1*/2 mutation carrier prevalence of TNBC patients was approximately 10%–30%. In this study, the prevalence of *BRCA1*/2 mutation carriers was 16.9%, consistent with the literature. The age at diagnosis of the patient group was 40.86±10.28 years; a statistically significant difference was not found between *BRCA1*/2 mutation non-carriers (40.5) and *BRCA1*/2 mutation carriers (37). In this study, the number of relatives with breast and ovarian cancer was significantly higher in the *BRCA1*/2 mutation carrier group than the non-carrier group. Logistic regression analysis showed that TNBC individuals with relatives with two or more breast and ovarian cancer have a 15-fold increase in the *BRCA1*/2 mutation carrier risk. Studies in the literature have shown that the lifetime risk of breast cancer in females is from 46%–87% in *BRCA1* mutation carriers and 38%–84% in *BRCA2* mutation carriers. In these studies, it was also observed that the risk of ovarian cancer up to the age of 70 is from 39%–63% in *BRCA1* mutation carriers and from 16.5%–27% in *BRCA2* mutation carriers (11-13). In addition to this dramatic increase in risk detected in breast and ovarian cancers, in *BRCA1*/2 mutation carriers, it has been reported in the literature that there is an increased risk in multiple other cancer types such as pancreas, colon, prostate, buccal cavity, pharynx, kidney, gall bladder, bile duct, cervix, uterine body, bone, stomach, and malignant melanoma. Although *BRCA1* and *BRCA2* genes both play tumor suppressor roles in the cell, cancers arising from mutations of each of these genes have specific clinicopathological structure. In the literature, these genotype-phenotype correlations were investigated many times. It was determined that observed cancer risks of each of these genes were not the same concerning the age of disease onset, sex, and the primary site of cancer origin (14-21). The diversity in research findings might be due to many reasons, such as insufficient samples, studies in geographically and ethnically different societies, and diversity in analysis systems.

In this study, relatives had 20 different cancer types based on the pedigree analysis of TNBC patients. Twenty-five of 65 patients had at least one relative with breast cancer. At least one relative of 49 patients had a cancer diagnosis (principally breast, lung, colon, stomach, prostate, other types). Regardless of the type of cancer, a significant relationship was found between the number of relatives diagnosed with cancer and *BRCA1*/2 mutation carrier status. According to the logistic regression model, it was predicted that the risk of carrying *BRCA1*/2 mutation would increase 1.3 times with an increase in the

Table 2. *BRCA1* and *BRCA2* genes analysis results

ID	Gene	Nuc/AA change	Loc	Func	ACMG scoring	dbSNP	Age/ Age of Dx	HPT	Ki-67	G	BBC	Cancer history on relatives
P3	*BRCA1*	c.4327C>T (p.Arg1443Ter)	Ex12	NS	Pat	rs41293455	50/49	IDC	70	3	-	2BC,1OC, 1GC, 1PrC, 1EC
P4	*BRCA1*	c.1961delA (p.Lys654SerfsTer47)	Ex10	FS	Pat	rs80357522	55/51	MC	75	3	-	3BC, 2CC, 1LC, 2PrC, 3MM, 1PC, 1EC
P14	*BRCA1*	c.5098delC (p.Leu1700Ter)	Ex16	NS	Pat	rs80357896	36/35	IDC	95	3	-	1BC, 1LC, 1PC
P21	*BRCA2*	c.8395delA (p.Arg2799AspfsTer22)	Ex19	FS	Pat	rs80359709	46/32	IDC	90	3	-	1BC, 1LC, 1BrC
P28	*BRCA1*	c.5507G>A (p.Trp1836Ter)	Ex22	NS	Pat	rs80356962	31/30	IDC	90	3	-	1BC, 1GC
P30	*BRCA1*	c.3844G>T (p.Glu1282Ter)	Ex10	NS	Pat	Novel	52/50	IDC	30	3	-	1BC, 1BrC, 1CC, 1BrC, 1GC,3 LC
P39	*BRCA2*	c.1773_1776delTTAT (p.Ile591MetfsTer22)	Ex10	FS	Pat	rs80359304	55/40	IDC	70	3	+	2BC, 1LC, 1EC, 1GC, 1LxC
P41	*BRCA1*	c.4307_4308delCT (p.Ser1436PhefsTer4)	Ex12	FS	Pat	rs397509161	30/27	IDC	90	3	-	3BC
P48	*BRCA2*	NM_000059:c.7710_7711delGG (p.Glu2571LysfsTer12)	Ex16	FS	Pat	Novel	38/37	IDC	80	3	-	-
P51	*BRCA2*	c.5969delA (p.Asp1990ValfsTer)	Ex11	FS	Pat	rs886038135	47/45	IDC	NA	NA	-	-
P60	*BRCA1*	c.5314C>T (p.Arg1772Ter)	Ex19	NS	Pat	rs80357123	30/26	IDC	40	3	-	1EC, 1CC

Loc: Localization; Ex: Exon; Func: Function; Nuc: Nucleotide; AA: Aminoacide; NS: Nonsense; FS: Frameshift; Pat: Pathogenic; Dx: Diagnoses; HPT: Histopathologic type; IDC: Invasive Ductal Carcinoma; MC: Medullary Carcinoma; G: Grade; NA: Not available; BBC: Bilateral breast cancer; BC: Breast cancer; OC: Ovarian cancer; GC: Gastric cancer; PrC: Prostate cancer; PC: Pancreas cancer; EC: Endometrium cancer; CC: Colon cancer; LC: Lung cancer; MM: Malign Melanoma; BrC: Brain cancer; LxC: Larynx cancer; ACMG: American College of Medical Genetics and Genomics

Table 3. Relationship of variables with *BRCA1/2* mutation carrier status

Variable	*BRCA1/2* non-carriers (n = 54)		*BRCA1/2* mutation carriers (n = 11)		p-value
	n	%	n	%	
Age					
≤40	18	33	5	46	0.443
>40	36	67	6	54	
Age at diagnosis					
≤40	27	50	7	64	0.409
>40	27	50	4	36	
Right/left					
Right	27	50	4	36	0.481
Left	19	35	6	55	
Bilateral	8	15	1	9	
Level of education					
Elementary school	21	39	6	55	0.394
High school	18	33	4	36	
University	15	28	1	9	
Chronic disease					
No	39	72	5	46	0.084
Yes	15	29	6	54	

Table 3. Continued

Variable	*BRCA1/2* non-carriers (n = 54)		*BRCA1/2* mutation carriers (n = 11)		p-value
	n	%	n	%	
Surgery history					
No	37	69	8	73	0.783
Yes	17	31	3	27	
Menstrual period					
Irregular	8	15	-	-	0.173
Regular	46	85	11	100	
Living place					
Rural	9	17	2	18	0.903
City	45	83	9	82	
Grade					
≤2	15	28	-	-	0.055
3	39	72	11	100	
Metastasis at diagnosis					
No	34	64	8	73	0.432
Yes (localized, regional, axiller)	19	36	3	27	
Marital status					
Single	5	9	2	18	0.628
Married	48	89	9	82	
Widow	1	2	-	-	
Number of children					
None	7	13	4	36	
1	10	19	-	-	0.058
2	31	57	4	36	
≥3	6	11	3	28	
The number of relatives with cancer	36	67	3	28	
None	13	24	4	36	0.021
1	5	9	4	36	
≥2					

χ^2-cross tables were used to examine the relationships between the two qualitative variables.
n: Number

Table 4. Comparison of parameters according to *BRCA1/2* mutation carrier status

Variable	*BRCA1/2* non-carriers (n = 54)		*BRCA1/2* mutation carriers (n = 11)		p-value
	$\bar{X}$ ± SD	Median	$\bar{X}$ ± SD	Median	
Age (year)	46±10	47.0	43±10	46.0	0.411
Age at diagnosis (year)	41±10	41.0	38±9	37.0	0.407
Ki-67	49±29	40.0	73±22	78.0	**0.022**
NOR with BC/OC	0±0	0.0	1±1	1.0	**0.006**
NOR with ATC	2±2	2.0	4±4	3.0	**0.047**

Independent Sample t-test (t-table value) for comparing the measurement values of two independent variables in data with normal distribution; Mann-Whitney U test (Z-table value) statistics were used for data that did not have a normal distribution; Significant p-values are shown in bold.
NOR: Number of relatives; BC: Breast cancer; OC: Ovarian cancer; ATC: All types of cancer; SD: Standard deviation; n: Number

Table 5. Logistic regression model for *BRCA1/2* mutation carrier risk status of relatives with breast/ovarian cancer

Variable	p-value	OR	95% Confidence interval (OR)* (min-max)	
FH of breast/ovary Ca - None	0.026	-	-	-
1	0.097	4.12	0.77	21.96
≥2	**0.008**	15.13	2.06	111.17
Constant	0.920	0.84	-	-

Significant p-values are shown in bold. *Binary logistic regression, Backward: LR model was used.
OR: Odds ratio; Ca: Cancer; FH: Family history; min: Minimum; max: Maximum

Table 6. Logistic regression model for *BRCA1/2* mutation carrier risk status of relatives with all types of cancers

Variable	p-value	OR	95% Confidence Interval (OR)* (min-max)	
FH of all types of cancers	0.031	1.31	1.03	1.68
Constant	0.000	0.09	-	-

Significant p-values are shown in bold. *Binary logistic regression, Backward: LR model was used.
FH: Family history; OR: Odds ratio; min: Minimum; max: Maximum

number of each relative with cancer for TNBC patients.

This study's limitations are that the sample group was not large enough, and co-segregation analysis could not be performed for all patients' relatives. Information about a cancer diagnosis in patients' relatives was obtained from the pedigree analysis, and pathological reports of most of them could not be reached. Also, environmental factors that may predispose relatives to cancer could not be investigated. In conclusion, TNBC is a heterogeneous cancer type that occurs at an early age, has a poor prognosis, and high histopathologic grade.

In this study, we investigated the relationship between TNBC and *BRCA1/2* mutation carrier status of 65 patients. We found a significant relationship between *BRCA1*/2 mutation carrier status, high Ki-67 index, and the number of relatives with cancer. In the future, further research is needed to determine the importance of these genes in TNBC and help elucidate the complex nature of TNBC.

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Ethics Committee Approval: The present study involved human participants, and it was conducted considering ethical responsibilities according to the World Medical Association and the Declaration of Helsinki. The independent Ethics Committee of the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital approved this study (no: 2020-02/536).

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

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: N.D.; Design: N.D.; Supervision: N.D.; Resources: N.D.; Materials: N.D., O.K.; Data Collection and/or Processing: N.D., O.K.; Analysis and/or Interpretation: N.D.; Literature Search: N.D.; Writing Manuscript: N.D.; Critical Review: N.D., O.K.

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Original Article

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Were We Able to Reduce Cardiac Doses in Breast Cancer Radiotherapy Over Time?

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ABSTRACT

Objective: In this study, we aimed to review the heart and left coronary artery doses over the years in patients who received breast cancer radiotherapy (RT).

Materials and Methods: A total of 436 breast cancer patients of 2 RT centers treated between the years 2010 and 2018 were included. The mean heart doses (HeartDmean-HDM) and left coronary artery mean doses (LDM) were analyzed using nonparametric tests. The conventional RT (CRT) was 50 Gy/2 Gy in 5 weeks, and the hypofractionated RT (HRT) was 40.05 Gy/2.67 Gy in 3 weeks. Boost was applied as 10–16 Gy/2 Gy for CRT and 10 Gy/2.5 Gy for HRT. An equivalent conventional total dose of 2 Gy/fraction (EQD2) was taken into account for HRT.

Results: HDM was 107±104 cGy, and LDM was 288±209 cGy for the entire group. HDM was significantly lower in patients with breast-conserving surgery (99±94 cGy) than that in those with mastectomy (128±124 cGy) ($p<0.001$). Field-in-field intensity-modulated RT technique significantly reduced the doses compared to volumetric applications (104±95 cGy vs 141±38 cGy; $p = 0.002$). HDM was significantly increased with lymphatic RT (132±58 cGy vs 112±115 cGy; $p<0.001$). The addition of internal mammary volumes significantly increased HDM ($p<0.001$). No significant effect of boost was observed ($p = 0.96$). For both CRT and HRT regimens, HDM values were significantly lower after the year 2014 (right side $p<0.001$, left side $p = 0.01$). In the left side CRT, HDM was 1.74 Gy before 2014 and 1.3 Gy after 2014 and 1.0 and 1.19 Gy, respectively, for the right side.

Conclusion: All efforts to reduce the cardiac doses will likely reduce long-term side effects.

Keywords: Breast cancer, radiotherapy, cardiac toxicity

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Key Points

- Cardiac toxicity is the most important cause of morbidity and mortality of breast cancer radiotherapy. The mean heart dose is the major predictor of this late side effect.
- The significant increase of the mean heart doses is observed after mastectomy, with the application of volumetric techniques and adding lymphatic irradiation to the treatment. The results were the same for both conventional and hypofractionated regimens.
- The significant reduction of mean heart doses could be achieved after 2014.

Introduction

Cardiac toxicity due to radiotherapy (RT) in breast cancer has been an issue which has been emphasized for many years. The risk begins within a few years after treatment and may continue to 15–20 years. Cardiac risk factors and some of the systemic treatments that patient receive contribute to this toxicity. Owing to the development of computed tomography and its integration into RT plans after the 1990s, the exact cardiac doses and their long-term effects could be more accurately observed (1). Over the years, cardiac and left main coronary artery doses due to breast RT were reviewed, and treatment practices were developed to reduce these doses. Studies published in the recent years showed that after 2014–2015, a significant decrease has been achieved. In this study, we aimed to review the heart and left coronary artery doses over the years in patients who received breast cancer RT.

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Materials and Methods

After the approval of ethical review board, Acıbadem University (decision no: 2020-03/04, date: 27.02.2020) 436 breast cancer patients of two different RT centers in Turkey treated between the years 2010 and 2018 were included. The impacts of variables as treatment side (left or right), fractionation, treatment volumes, energy used, presence of respiratory control, presence of boost, type of surgery [mastectomy or breast-conserving surgery (BCS)], and the treatment date on the mean heart doses (HeartDmean-HDM) and left coronary artery mean doses (LDM) were retrospectively analyzed. EQD2 was taken into account by accepting heart alpha/beta ratio as 3 for hypofractionated regimens.

The distribution of left and right breast cancers were almost equal (49% vs 51%). The majority of the patients had BCS (72.5%). The irradiation technique, to a great extent, was field-in-field intensity-modulated RT (FIF-IMRT) (97.2%). Respiratory control was performed in 169 patients (38.8%). More than half of the patients received breast RT only (51.8%). Mammaria interna irradiation was performed in 138 patients (31.7%). The percentage of patients with a boost was 56% (Table 1).

Statistical analysis

The impact of variables was analyzed using nonparametric tests (IBM SPSS Statistics V20).

Results

When all patients were evaluated together, the average HDM was determined to be 107 cGy [standard deviation, (SD): 104 (1–1290)], and LDM was 288 cGy [SD: 209 (0–1124)]. HDM was significantly lower in patients with BCS (99±94 cGy) than that in those with mastectomy (128±124 cGy) (p<0.001). FIF-IMRT technique significantly reduced the doses compared to the volumetric applications (dynamic IMRT and volumetric arc therapy) (104±95 cGy vs 141±38 cGy; p = 0.002). HDM was significantly higher in patients who received lymphatic volume irradiation in addition to whole breast/chest wall (128±58 cGy vs 90±115; p<0.001). The addition of internal mammary volumes to supra and axillary lymphatics significantly increased HDM in patients receiving lymphatic RT (p<0.001). No significant effect of boost was observed (p = 0.96).

When HDM values were evaluated together for all years, the "time" factor was accepted as the years before and after 2014 since nonparametric tests indicated a significant change in this year. The treatment plans were also evaluated separately according to conventional and hypofractionated RT and also according to treatment side (left vs right breast).

A total of 163 patients received RT to right breast with conventional fractionation. BCS was applied to 98 (60.1%). The FIF-IMRT rate was 97.5%. A total of 80 patients received whole breast/chest wall irradiation (WBI/CW) (49.1%), 46 patients (28.2%) received WBI/CW and were irradiated at any lymphatic volume(s), and 37 patients (22.7%) were irradiated at all lymphatic volumes along with WBI/CW. A total of 53 (32.5%) patients were treated before 2014 and 110 (67.5%) in 2014 and after [HDM mean, median and SD values were 101 cGy, 95±39 cGy, and 71 cGy, 57±119 cGy, respectively, for before and after 2014 (p<0.001)]. The addition of internal mammary volumes significantly increased HDM for patients with conventionally treated right breast cancer (p = 0.047). There was no difference in terms of type of surgery, respiratory control, and addition of boost.

There were 61 patients who received right breast irradiation with hypofractionation. No analysis was made for surgery, respiratory control, lymphatic RT, and boost due to the inequality of distribution between the comparison groups. HDM mean, median doses, and SD values were significantly different for patients treated before 2014 and after 2014; 66 cGy, 58±37 cGy vs 38 cGy, 33±14 cGy (p<0.001).

Table 1. Treatment characteristics of the patients

	Left-sided CRT (n = 177)	Right-sided CRT (n = 163)	Left-sided HRT (n = 35)	Right-sided HRT (n = 61)
Operation	BCS = 126 (71%) M = 51 (29%)	BCS = 98 (60%) M = 65 (40%)	BCS = 34 (97%) M = 1 (3%)	BCS = 58 (95%) M = 3 (5%)
RT technique	FIF-IMRT = 169 (95%) Volumetric R = 8 (5%)	FIF-IMRT = 160 (98%) Volumetric RT = 3 (2%)	FIF-IMRT = 35 (100%) Volumetric RT = 0	FIF-IMRT = 61 (100%) Volumetric RT = 0
Breath hold	Present = 107 (60%) Absent = 70 (40%)	Present = 29 (18%) Absent = 134 (82%)	Present = 30 (86%) Absent = 5 (14%)	Present = 3 (5%) Absent = 58 (95%)
Lymphatic volume irradiation	Present = 102 (58%) Absent = 75 (42%)	Present = 83 (51%) Absent = 80 (49%)	Present = 2 (6%) Absent = 33 (94%)	Present = 6 (10%) Absent = 55 (90%)
MI irradiation	Present = 71 (40%) Absent = 106 (60%)	Present = 67 (41%) Absent = 96 (59%)	Present = 1 (3%) Absent = 34 (97%)	Present = 2 (3%) Absent = 59 (97%)
Boost	Boost = 116 (65%) No boost = 61 (35%)	Boost = 82 (50%) No boost = 81 (50%)	Boost = 18 (51%) No boost = 17 (49%)	Boost = 28 (46%) No boost = 33 (54%)
Time Interval	<2014 = 62 (35%) ≥2014 = 115 (65%)	<2014 = 53 (32%) ≥2014 = 110 (68%)	<2014 = 5 (14%) ≥2014 = 30 (86%)	<2014 = 11 (18%) ≥2014 = 50 (82%)

RT: Radiotherapy; CRT: Conventional RT; HRT: Hypofractionated RT; BCS: Breast-conserving surgery; M: Mastectomy; FIF-IMRT: Field-in-field intensity-modulated radiotherapy; MI: Mammaria interna; n: Number

A total of 177 left-sided patients received RT with conventional fractionation. Most of them were BCS (71.2%). FIF-IMRT was applied in 95% of patients. Respiratory control was applied in 107 patients (60.5%). Lymphatic RT was absent in 75 patients (42.4%). A total of 62 patients were treated before 2014. HDM mean, median, and SD values before 2014 vs 2014 and after were 174 cGy, 161±68 cGy vs 130 cGy, and 127±48 cGy, respectively (p<0.001). HDM values were significantly lower for patients with BCS (p = 0.001), without any lymphatic volume irradiation (p<0.001), or no mammaria interna RT (p<0.001). Similarly, LDM was significantly lower if there was BCS (p = 0.001), there was no lymphatic RT (p<0.001), and there was no internal mammary RT (p<0.001). LDM mean, median, and SD values were also significantly higher for patients treated before 2014 (390 cGy, 337±180 cGy vs 429 cGy, 406±154 cGy, respectively) (p = 0.012). Statistical significance was not determined in other parameters evaluated.

Surgery, nodal RT, MI RT, and RT technique could not be evaluated in 35 patients who had left HRT because of distribution inequality. Five patients were irradiated before 2014, and the remaining 30 were irradiated in or after 2014. The HDM mean for patients treated before 2014 was 302cGy, and for patients treated in or after 2014, the HDM mean was 115 cGy (p = 0.01) (Table 2 and Table 3).

Table 2. Mean heart doses (median cGy ± standard deviation)

	Left-sided CRT (n = 177)	Right-sided CRT (n = 163)	Left-sided HRT (n = 35)	Right-sided HRT (n = 61)
Operation	BCS = 127±58 M = 159±57	BCS = 61±30 M = 76±154	BCS = 84±229 M = null	BCS = 37±17 M = 35±76
RT technique	FIF-IMRT = 138±60 Volumetric RT = 149±31	FIF-IMRT = 67±34 Volumetric RT = 147±68	FIF-IMRT = 84±226 Volumetric RT = null	FIF-IMRT = 37±22 Volumetric RT = null
Breath hold	Present = 134±49 Absent = 149±71	Present = 67±42 Absent = 70±110	Present = 83±173 Absent = 122±424	Present = 32±33 Absent = 37±22
Lymphatic volume irradiation	Present = 156±60 Absent = 113±53	Present = 68±38 Absent = 70±139	Present = 106±21 Absent = 84±233	Present = 54±47 Absent = 35±17
MI irradiation	Present = 158±56 Absent = 124±58	Present = 72±38 Absent = 63±128	Present = null Absent = 84±229	Present = 108±74 Absent = 35±17
Boost	Boost = 128±60 No boost = 153±57	Boost = 64±138 No boost = 73±36	Boost = 84±223 No boost = 84±236	Boost = 32±10 No boost = 47±27
Time interval	<2014 = 161±68 ≥2014 = 127±48	<2014 = 95±39 ≥2014 = 57±119	<2014 = 123±424 ≥2014 = 83±173	<2014 = 58±37 ≥2014 = 33±14

RT: Radiotherapy; CRT: Conventional RT; HRT: Hypofractionated RT; BCS: Breast-conserving surgery; M: Mastectomy; FIF-IMRT: Field-in-field intensity-modulated radiotherapy; MI: Mammaria interna; n: Number

Table 3. Mean heart doses changing along the years according to treatment side and schedule

	Before 2014 Heart Dmean Mean, median; SD (min-max) cGy	2014 and after Heart Dmean Mean, median; SD (min-max) cGy	p-value
Right side conventional	n = 53 101; 95±39 (1–268)	n = 110 71; 57±119 (9–1290)	<0.0001
Right side hypofractionated	n = 10 66; 58±37 (32–161)	n = 51 38; 33±14 (12–89)	0.001
Left side conventional	n = 62 161; 174±68 (74–388)	n = 115 127; 130±48 (1–357)	p<0.0001
Left side hypofractionated	n = 5 302; 123±424 (84–1060)	n = 30 115; 83±173 (55–1030)	0.01

SD: Standard deviation; min: Minimum; max: Maximum; n: Number

Discussion and Conclusion

The contribution of RT to breast cancer-related survival is well-known (2, 3). In prolonged survival, late side effects of RT may increase the patients' morbidity and mortality. It may cause an increase in cardiac mortality by creating ischemic heart disease especially in left breast irradiation (4). Considering that the cardiac side effects occur in a period of up to 15-20 years after RT, it should be remembered that the RT technique applied in studies examining this toxicity belongs to about 10 years before.

In the old meta-analysis conducted by Cuzick et al. (5) which included studies comparing surgery and surgery + adjuvant RT, it was revealed that cardiac deaths were higher with RT in 10 years. However, decreased breast cancer deaths with RT contributed to the overall survival rates (49.5 fewer breast cancer deaths versus 64.2 cardiac death increase). In a more recent meta-analysis examining studies between 1966 and 2015, data of over 1 million patients were used, the relative risk of coronary artery disease was 1.30, and the relative risk of cardiac mortality was 1.38 in patients receiving RT (6).

The case-control study conducted by Darby et al. (4) including the years 1958–2001 in patients who received RT in Sweden and Denmark is a landmark study in terms of RT-related ischemic heart disease. This study revealed the dose-response relationship and showed that every 1 Gy increase in the average heart dose increased the risk of ischemic heart disease by 7.4% (4). This study also states that the mean heart dose is a better marker for evaluating major coronary complications. HDM was found to be higher in left side irradiation (4), and the risk of cardiac death was consequently greater (6).

It can be observed that HDM reported by different studies varies throughout the years. As an example, in the 2013 study of Darby et al. (4), covering the years 1958–2001, the left side HDM was 6.6 Gy, and the right side was 2.9 Gy, and the doses increased significantly when lymphatic irradiation and especially MI RT were performed. The study, in which Taylor et al. (7) reviewed 149 studies, covering the years 2003-2013, found that the left side HDM was 5.4 Gy and the right-side HDM 3.3 Gy (7).

A better understanding of cardiac toxicity has led to advances in current techniques for lowering heart doses and accelerated the applications of better contouring (8), respiratory-controlled RT (9), and different RT applications (4).

In the article published by the Michigan Radiation Oncology Quality Consortium (MROQC), 4,688 patients, irradiated between 2012 and 2015, were examined. These patients were evaluated for left- versus right-sided RT and conventional versus accelerated RT. In the left-sided irradiation, HDM decreased significantly over the mentioned 4-year period (for conventional RT, 2.19 Gy in 2012, 1.65 Gy in 2015; for accelerated RT, 1.70 Gy in 2012, 1.22 Gy in 2015). In conventional RT patients, excessive breast separation, nodal irradiation, MI irradiation, the use of IMRT, and additional boost increased HDM. Separation, boost, and IMRT use were found to be effective in the increase of HDM in those with accelerated RT (10).

Another more recent review from Canada examined 99 studies conducted between 2014 and 2017 after Taylor et al. (7) (11). The average HDM in this study is 3.4 Gy and is lower than that of Taylor's study (5.2 Gy). An increase in HDM doses has been shown with lymphatic irradiation, additional boost, and the use of VMAT and IMRT instead of tangential RT. In addition, a significant decrease was observed in HDM in the left-sided irradiation each year; the average HDM was 4.6 Gy in 2014, and it decreased to 2.6 in 2017.

In Taylor's review, the average HDM of left side between 2003 and 2013 was 5.4 Gy, while in the 2014–2017 Canada review, it was 3.6 Gy. The right-side average HDM is 3.3 Gy in Taylor's compilation and 1.9 Gy in Canada. These doses appear higher than in the Michigan study.

In our study, while the average HDM doses decreased between 2010 and 2018, the threshold was found as 2014. In conventional RT applications on the left side, the mean HDM was 1.74 Gy before 2014 and 1.3 Gy after 2014 and 1.0 and 1.19 Gy, respectively, for the right side. These values are lower than the Taylor and Canada reviews and are more compatible with those of the Michigan study. Lymphatic RT and MI irradiation significantly increased the mean HDM doses as in other studies. Reduced HDM doses were achieved with FIF-IMRT as in the Canada study, but addition of boost dose did not statistically differ HDM unlike MROQC study.

However, since the right-left side, conventional and hypofractionated regimens were evaluated separately, and the number of patients per group led to distribution inequality in some important parameters such as boost application and was not found suitable for statistical evaluation. Significance can be gained with higher number of patients.

At least 5–10 years of long-term follow-up is needed to determine whether there are fewer cardiac events with decreasing heart doses and if local recurrence rates increase in return. We haven't reached that follow-up time yet. So, this could be the topic for subsequent studies.

As the current evidence reveals, all effort should be put into lower cardiac doses as much as possible.

Ethics Committee Approval: This study was approved by the Acıbadem University Ethics Committee (decision no: 2020-03/04, date: 27.02.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: P.A., A.A., N.B.; Design: P.A., A.A., N.B.; Supervision: P.A., A.A., N.B.; Materials: P.A., L.K., A.A., N.B.; Data Collection and/or Processing: P.A., L.K.; Analysis and/or Interpretation: P.A.; Literature Review: N.B.; Writing: P.A., N.B.; Critical Review: A.A., N.B.

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Original Article

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Breast Cancer Incidence Reduction in Women Treated with Subcutaneous Testosterone: Testosterone Therapy and Breast Cancer Incidence Study

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ABSTRACT

Objective: Testosterone (T) therapy has been shown to be breast protective in both pre- and post-menopausal patients. Additionally, estradiol (E) does not cause breast cancer (BC) in the majority of the world's literatures. This study aimed to investigate the incidence of invasive BC (IBC) in pre- and post-menopausal women treated with T therapy and T in combination with E (T/E).

Materials and Methods: Since January 2010, a total of 2,377 pre- and post-menopausal women were treated with T or T/E implants. IBC rates were reported based on newly diagnosed IBC cases in the total study. Total cases divided by the total sample size and years in study was expressed as an incidence per 100,000 person-years (P-Ys). The BC incidence was compared with age-specific Surveillance Epidemiology and End Results (SEER) incidence rates.

Results: As of October 2020, 14 cases diagnosed with IBC have been found in 9,746 P-Y of follow up for an incidence of 144 cases per 100,000 P-Y, substantially less than the age-specific SEER incidence rates (223/100,000), placebo arm of Women's Health Initiative Study (330/100,000), and never users of hormone therapy from the Million Women Study (312/100,000).

Conclusion: T and/or T/E pellet implants significantly reduced the incidence of BC in pre- and post-menopausal women. The addition of E did not increase the incidence over using T alone. This is the second multi-year long-term study demonstrating the benefits of T therapy in reducing the incidence of IBC.

Keywords: Pellet, testosterone pellet implantation, estradiol, breast cancer risk, hormone replacement therapy

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Key Points

- In the United States, 240,000 women will develop breast cancer (BC) annually and 40,000 will die from the disease.
- Testosterone hormone optimization has been shown to reduce the incidence of invasive breast cancer in women.
- This study (The Testosterone Therapy and Breast Cancer Incidence Study) is the largest long term study to further demonstrate this benefit and shows a reduced incidence of IBC in women taking testosterone and estradiol sub-cutaneous hormone pellet therapy.

Introduction

Hormone replacement therapy (HRT) is a type of treatment that involves taking hormones to prevent or treat certain medical conditions and/or symptoms associated with female menopause and pre-menopause. These symptoms can include hot flashes, insomnia, vaginal atrophy, accelerated skin aging, vaginal dryness, decreased muscle mass, sexual dysfunction, night sweats, fatigue, joint pain, and others. These symptoms are in large part related to diminished levels of sex hormones. Improvement of symptoms is achieved through hormone replacement and optimization. Furthermore, long-term benefits of HRT include reduced risk for bones, heart, brain, and different cancers (1-3).

In the United States, 240,000 women developed breast cancer (BC) annually and 40,000 will die from the disease (4). The lifetime risk of developing BC is 1 in 8 (5). HRT for menopause women has been used mostly in western countries, with about 600 million woman-years of use since 1970.

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Some articles have shown excess BC risks, with duration of use that were greater for estrogen-progestogen (EPT) than estrogen (ET) only preparations (6, 7). In contrast, the Women's Health Initiative (WHI), the largest long-term randomized clinical trial of combined equine ET alone (CEE alone) or EPT, found a significantly higher risk of developing invasive BC (IBC) among women using EPT, whereas a lower risk was observed in CEE alone arm (8). Others have shown a reduction in BC risk (9). Variations and differences in outcomes may be due to heterogeneity in studies including but not limited to Body Mass Index (BMI), age at onset of HRT, hysterectomy status, bio-identical versus synthetic hormone formulations, and route of administration (oral vs non-oral). Adding to the conundrum, the risk associated with EPT differed according to the progestin used, resulting in higher risk with medroxyprogesterone acetate, levonorgestrel, and norethisterone [odds ratio (OR): 1.87, confidence interval (CI): 1.71–2.05; OR: 1.79, CI: 1.68–1.90; and OR: 1.88, CI: 1.79–1.99, respectively] and lower with dydrogesterone (OR: 1.24, CI: 1.03–1.48) after 5 years of therapy (10).

Excess risk associated with EPT duration was seen across all and hormone receptor subtypes. In addition, duration of EPT use was linked to excess overall BC risk and to ductal (DCIS) and lobular cancer *in situ* (LCIS). For ET users, no statistically significant differences were seen for either DCIS or LCIS (7).

Certain types of ET showed to stimulate breast tissue and increase the risk of BC. Prior to the current study, only one long-term study was published on the benefits of testosterone (T) therapy in women (9). The risk of developing BC showed to be increased by elevated endogenous ET levels (11). Androgens showed to counteract the proliferative effects of ET in mammary tissue (12). Breast tissue extirpated from pre- and post-menopausal women also has demonstrated the inhibitory effects of T on breast cell proliferation (13, 14). The corollary has also been reported that bio-available T is significantly lower in women with BC, which supports the protective role that hormone optimization with T affords to patients (15). Adherence to T hormone pellet therapy has furthermore shown to reduce the incidence of BC from 330 per 100,000 women years (placebo arm of the WHI) to 165 per 100,000 women years in the Dayton study in patients using T and/or T with anastrozole subcutaneous hormone pellet therapy (9).

T therapy has been increasing 12× worldwide since year 2000. Benefits to the bones, heart, and brain have been reported (1-3). The current study is a retrospective observational study that was specifically designed to investigate the incidence of BC in women treated with subcutaneous T and/or T/E implants for clinical syndrome of T deficiency and/or menopausal state.

Materials and Methods

Study design, setting, and participants

All data analyzed was drawn from patients at the Institute for Hormonal Balance (IHB) as part of an Institutional Review Board (IRB) exempt study that retrospectively investigated the incidence of BC in women treated with subcutaneous T or T/E implants from January 2010 to 2020.

Data for analysis was identified based on presentation to the clinic with symptoms of T and/or ET deficiency including hot flashes, night sweats, insomnia, depressive mood, irritability, anxiety, fatigue, memory loss, menstrual or migraine headaches, vaginal dryness, reduced libido, and urinary symptoms including incontinence, muscle pain, and/or bone loss (5). Both pre- and post-menopausal patients were considered for retrospective analysis. Estradiol (E) implants were utilized if laboratory testing indicated necessity for E2 administration (follicle-stimulating hormone (FSH) >23 and last menstrual period (LMP) >6 months prior). T administration was offered if clinical symptoms for T deficiency were present and laboratory testing confirmed a serum level of <70 ng/dl. All female patients opting to receive human identical hormone pellet therapy as their method for replacement were considered for analysis in this study. If patients were post-menopausal, defined as FSH >23 and no longer menstruating, requiring E subcutaneous pellets with or without oral micronized progesterone based on hysterectomy status, their data was included from the study. Women with a personal history of BC were excluded from data analysis. No patient was excluded from analysis based on age, prior hormone use, oral contraceptive use, endometrial pathology, breast density, BC family history, menopausal status, or BMI. Mammography and clinical breast exam were not protocol determined. Screening mammograms were not required for data from a patient to be considered for analysis. Patients who had received T implants prior to the IRB exemption date were also not excluded from analysis. Study size was therefore not predetermined. The incidence of BC in our study population was to be compared to historical controls (e.g., placebo control group of WHI combined arm) (8), as well as age-specific Surveillance Epidemiology and End Results (SEER) data. The SEER data is from www.seer.cancer.gov and is an authoritative source for cancer statistics in the United States. It is notable that SEER data for IBC in women age 40–64 years has changed very little over the past 17 years (16).

Subcutaneous implants, the evolution of T therapy in clinical practice, and T with and without E implants

The T and E implants used at the Institute for Hormone Balance and its satellite offices are compounded by a 503b outsourcing pharmacy in Denton, Texas. They are composed of USP T and steric acid or USP E and steric acid (5.21%). A proprietary Food and Drug Administration (FDA) approved process compresses substrates into 3.1 mm (diameter) cylinders, sealed in glass ampoules, and sterilized by E beam sterilization. Sterile implants are inserted into the subcutaneous tissue of the upper gluteal area or lower abdomen through a small anesthetized incision using a stainless-steel sterile trocar or a disposable trocar kit.

The IHB has been involved in bio-identical HRT over the past 24 years. Oral ET therapy and ET and/or T creams were used in majority of patients needing replacement through 2007. The practice augmented our armamentarium of HRT adding the use of subcutaneous hormone pellet therapy in 2008. From our experience, subcutaneous hormone pellet therapy provides improved relief of symptoms with fewer side effects than more traditional HRT therapies. The success of T implants in treating symptoms of pre- and post- menopausal patients was additionally shown by Glaser et al (17). The IHB developed a proprietary dosing computerized algorithm for pellet dosing based on patient demographics, symptoms, laboratory values, and medical co-morbidities.

Data analytics and patient follow up

From January 2010 through October of 2020, data from the Testosterone Therapy and Breast Cancer Incidence Study was entered into a secure, custom tracking App, using Microsoft Azure App Services and MS SQL Database integrated with a proprietary dosing site and

industry leading Pharmacy Dispensing software (BioTracker®). Patient data was also entered into an electronic medical record program with all history, laboratory data, and pellet insertion dosage, including start and end dates. Most patients returned for subsequent insertion at 90–120 days based on symptom return. Follow-up calls and serum lab testing were performed at 4–6 weeks after first insertion and then annually. Patients were evaluated at each visit and T and ET dosing was adjusted based on clinical symptom improvement and secondary responses reported. All patients no longer receiving therapy or those on therapy agreed to contact the office for any subsequent diagnosis of BC. All patients were contacted if they did not return for pellet therapy after 365 days. This served as an end date, and person-year (P-Y) would no longer accrue. They were screened for BC and any side effects arising from pellet therapy and reminded to report any IBC diagnosis in the future. In year 9, all patients underwent chart reviews to evaluate subsequent diagnosis of IBC. All patients who discontinued therapy at some point during the study (78% of the total enrolled) were contacted 1 year from their last insertion. The practice, in addition, performed follow up after obtaining suspicious mammogram results and surgical pathology reports to confirm the diagnosis and type of IBC.

Statistical analysis

BC rates are reported as number of newly diagnosed cases (unadjusted and un-weighted) divided by the total P-Ys of "at risk" population under observation. P-Ys of observation for each participant was calculated from the date of first T pellet insertion for the participant up to the date of cancer detection or therapy end date (1 year for those who discontinued therapy or latest contact date for those still under therapy), whichever came first and dividing that by 365. The program logic accurately and continually tracks the number of P-Ys based on the above logic for each participant and calculates a running sum (cumulative total) across the group.

To evaluate adherence rates, data submitted through BioTracker® was used to calculate the adherence rate of pellet use among participants over the study duration. The continuation rate is defined as the incidence of patient undergoing an implant procedure to have a subsequent implant procedure within 12 months of the initial procedure. BioTracker® preserved the database for retrospective analysis.

The incidence of BC was calculated per 100,000 p-y so that our results could be compared to the incidence of BC in published historical controls, as done in other studies as well as published BC incidence rates (8, 9, 15, 16, 18) (Table 1).

Utilizing SEER incidence rates, the expected BC incidence rate for our intent-to-treat group was calculated from the age distribution of enrolled patients (Graph 1). IBC rates from the Testosterone Health Initiative were compared to the age-adjusted SEER BC incidence rates published over nearly the same time frame.

Results

Patient demographics

As of December 2013, a total of 2,377 patients were identified as part of our retrospective analysis. This data showed that 19% of patients discontinued pellet therapy after the initial pellet insertion. Specific reasons for discontinuation after the initial pellet insertion were not captured as part of the data acquisition.

Table 1. Breast cancer cases in women using testosterone (T) or T with estradiol (T/E) compared with major studies using estrogen (ET), progestin (P) therapy, E/P/T/, E/T, past users, never users, and SEER incidence rates

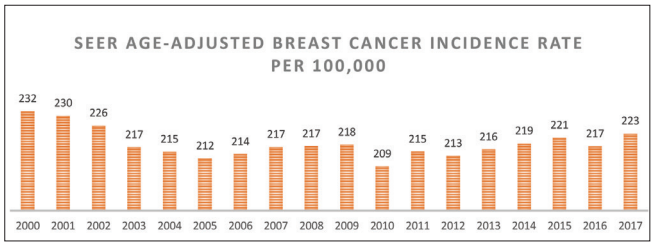
Study	Number of the Patients	Cases per 100,000 p-y	Years observed
The Testosterone Therapy and Breast Cancer Incidence Study (current study)			
T, T + E	2,377	144	9
Dayton Study (5)			
T, T + AI	1,267	165	10
WHI, RCT (8)			
Placebo	8,102	330	10.7
E alone	10,000	260	10.7
E + P	8,506	380	5.2
MWS (16)			
Never users	513,272	312	14
E alone, E + P	394,697	501	14
Adelaide (13)			
T + E	161	115	5.9
T + E + P	347	293	5.9
SEER (14)		223	-

AI: Anastrozole; WHI: Women's Health Initiative; RCT: Randomized controlled trial; MWS: Million Women Study; SEER: Surveillance Epidemiology and End Results

In the T arm, 640 women received more than one round of T pellet therapy and were therefore eligible for analysis. In addition, 1,737 patients received T and E pellet therapy for more than one round and were eligible for analysis (Chart 1).

The majority of patientswhich is >90% were accrued into the study by year 4. The mean number of years since first T implant was 8.8 years (range: 4.1–12.7). The youngest patient was 29 years old and the oldest was 87 years old (range: 29–87 years).

In Table 2, patient demographics are listed at the time of entry to the Testosterone Therapy and Breast Cancer Incidence Study. Our population was drawn from a group of long-term older gynecologic patients from the local population of the four IHB sites from which data were drawn from analysis as summarized in Table 2. The group was neither at an increase or decrease risk of IBC based on demographics. The mean age at first T pellet insertion was 58.7±8.0 years. 76% of patients were menopausal, with 2/3 of them having their uterus extirpated; 23% were pre/perimenopausal; and 28% had a positive family history of BC.



Graph 1. Breast cancer recent trends in SEER age-adjusted incidence rates, 2000–2017

All races (including Hispanic), ages: 40–64, all stages, delay-adjusted rates

SEER: Surveillance Epidemiology and End Results

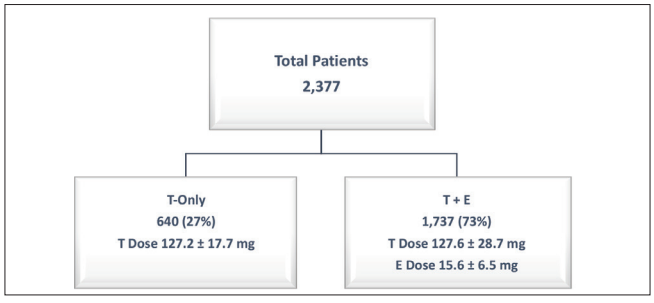


Chart 1. Accrued Patients for analysis and dosing comparison

T: Testosterone; E: Estradiol

Table 2. Patient demographics

Patient demographics	
Participants accrued (n)	2,834
Eligible for analysis, ITT	2,377
Completed only 1 round of pellets	457
Age at first implant, year	
ITT	58.7±8.0
Completed only 1 round of pellets	56.7±8.3
Menopausal (%)	76.8
Surgical (%)	66
Natural (%)	34
Pre/perimenopausal (%)	23.2
Family history of breast cancer (%)	28
BMI (kg/m^2)	27.2±5.3

ITT: Intent-to-treat; BMI: Body mass index; n: Number

BC incidence

As of October 2020, 14 IBC cases were diagnosed out of the 2,377 women in the use Testosterone Therapy and Breast Cancer Incidence Study (Table 3). These women all received more than two rounds of T implant therapy. This calculation based on P-Y of therapy adjusted to 100,000 P-Y of therapy resulted in an incidence of 144/100,000 P-Y.

Testosterone Therapy and Breast Cancer Incidence Study vs SEER and historical controls

A marked reduction in IBC cases was found in our accrued study group compared to the age matched SEER expected number of BC cases (14 vs 48 cases). The incidence rate for Testosterone Therapy and Breast Cancer Incidence Study was 144/100,000 vs 223/100,000 for the SEER data. Alternatively, one could compare our data to the placebo arm of WHI. Doing so, a marked reduction is observed in IBC cases in our accrued study group. We again accrued 14 cases of IBC vs 71 expected from the placebo arm of WHI. The incidence rate for Testosterone Therapy and Breast Cancer Incidence Study was 144/100,000 vs 330/100,000 for the WHI placebo patient arm (Table 1).

Characteristics of IBC study group (Table 3)

A total of 14 patients with reported and diagnosed IBC are presented in Table 3. All tumors were identified with mammography. The mean age at first T Therapy was 54.3±7.4 years. The mean age at diagnosis was 59.0±6.2 years. The mean length of therapy prior to diagnosis was 4.6 years (range: 1.2–10.5 years). Three of 14 patients with IBC had history of smoking; 12 of 14 IBC were DCIS and two were LCIS; and 13 of 14 BCs were ER+/PR+.

Discussion and Conclusion

Testosterone Therapy and Breast Cancer Incidence Study, a 9-year retrospective study, demonstrated a 35.5% reduction in IBC in both T and T/E hormone pellet implant users compared to age-specific SEER incidence rates (223/100,000). This study was done in nearly parallel fashion with the Dayton study using T and/or T/Anastrozole pellets (9). The Dayton experience also resulted in a significant lowered incidence of IBC in T implant users.

Subcutaneous T implants have been used to treat T deficiency in women since 1937 (19, 20). Additionally, T implants have been used to treat IBC (21). T is increasingly recognized as a vital hormone in women. In 2018, an International Consensus Group met regarding the use of T in women and unanimously agreed that T was the most important hormone for women regardless of the decade of life (22). By age 40, women have reduced their production of T by 50% and mostly are T deficient (23).

T promotes downstream physiological processes via functional androgen receptors (ARs) that are located in almost all tissues, including the breast, heart, blood vessels, gastrointestinal tract, brain, bladder, uterus, vagina, ovaries, skin, bone, bone marrow, muscle,

Table 3. Patient data diagnosed with invasive breast cancer for the duration of the study

Patient	Age at 1st TTY	BMI	Smoker	FH IBC	Detection	Hysterectomy	IBC type	Date of diagnosis	Receptor status
1	50.4	26.0	Y	Y	Mammo	No	Invasive ductal carcinoma	1/15/2020	ER+/PR+
2	45.9	26.2	N	N	Mammo	No	Invasive ductal carcinoma	6/3/2019	ER+/PR+
3	50.4	26.0	N	Y	Mammo	No	Invasive ductal carcinoma	1/3/2016	ER+/PR+
4	41.0	19.9	N	N	Mammo	Yes	Invasive lobular carcinoma	10/18/2018	ER+/PR+
5	51.4	45.4	N	N	Mammo	No	Invasive lobular carcinoma	8/1/2018	ER+/PR+
6	53.8	23.9	N	N	Mammo	Yes	Invasive ductal carcinoma	7/15/2019	ER+/PR+
7	59.8	29.9	N	Y	Mammo	Yes	Invasive ductal carcinoma	2/3/2017	ER+/PR+
8	49.7	26.9	Y	Y	Mammo	Yes	Invasive ductal carcinoma	7/6/2018	ER+/PR+
9	70.8	22.9	N	N	Mammo	No	Invasive ductal carcinoma	8/14/2013	ER-/PR-
10	44.3	20.6	N	N	Mammo	No	Invasive ductal carcinoma	9/27/2018	ER+/PR+
11	52.3	27.0	N	N	Mammo	No	Invasive ductal carcinoma	10/10/2018	ER+/PR+
12	57.0	25.8	N	Y	Mammo	No	Invasive ductal carcinoma	9/20/2014	ER+/PR+
13	59.0	31.0	N	Y	Mammo	Yes	Invasive ductal carcinoma	10/20/2012	ER+/PR+
14	58.6	33.2	Y	N	Mammo	No	Invasive ductal carcinoma	3/7/2014	ER+/PR+

FH: Family history; IBC: Invasive breast cancer; Y: Yes; N: No; BMI: Body mass index; ER: Estrogen receptor; PR: Progesterone receptor; TTY: Testosterone Therapy, year

joints, and adipose tissue. Use of the validated Menopause Rating Scale questionnaire has yielded objective evidence that T treatment significantly reduces symptoms in pre- and post-menopausal women (17).

In order to reduce cardiovascular disease, Alzheimer's disease, osteoporosis, and certain types of cancer (e.g., BC), a safe and effective route of administration for T is needed (20). Clinical studies in primates, *in vitro* evidence suggest that T androgen receptor complex (T-AR) is anti-proliferative that counteracts the stimulatory effects of ET (12). In addition, studies have shown in humans that T-AR downregulates the ER α receptor, is antiproliferative, and increases apoptosis of BC cell lines (3, 24). In 2014, neoadjuvant hormone therapy utilizing T implants demonstrated a significant clinical response rapidly decreasing the volume of an IBC followed by ultrasound surveillance (21).

At this time, no other route of delivery for T has demonstrated a reduction in the incidence of IBC. Most of the studies utilizing transdermal routes of administration were short in duration and failed to show the benefits seen with subcutaneous T hormone pellet therapy (25). The physiology of T implants allows more consistent steady state serum levels compared to other modalities, and as such the benefits in reducing IBC may not extend to oral or transdermal T delivery methods. The controversy over serum levels of T in the Dayton study and ours should be laid to rest at this point. In 2002, the Princeton Group published their findings that normal T levels for women are not established (26). Glaser and Dimitrakakis (24) published data with the rationale and efficacy of higher peak serum levels and safety of these levels in women. It has been established that T deficiency in women is a clinical syndrome and the inter-patient variability to resolve symptoms is basically inconsequential (20). Most recently, current authors have submitted for publication a 7-year study titled Low Complication Rates of T and E Implants for androgen and ET Replacement Therapy (ERT) in over one million procedures. Complications in women were <1% even though the peak serum levels were often in the lower range of normal for endogenous T in males (Under review).

A major strength of this study is that pellet therapy has an extremely high continuation rate, >81% (27). As such, the ability to evaluate patients at each office visit allows for improved maintenance of reinsertion intervals and improved screening for mammogram compliance. It also allowed for tracking any changes in medical diagnoses and/or adverse events. Additional strength of this study is the large sample size, in fact the largest reported on IBC prevention in the world literature. The single practice sample pool and limited number of practitioners allowed for consistency in therapy, record keeping, and tracking of adverse events.

A major limitation of this study is the self-reporting of patients that could lead to a selection bias and underreporting. There are several minor limitations of this study. The co-administration of E could have led to an increase in IBC theoretically; however, this was not the case in Adelaide's study (15), nor this one. The controversy surrounding E as a causative agent in BC persists nearly 20 years after WHI. It is beyond the scope of this paper to elaborate about all studies, but the argument on both sides is well expanded upon in Avrum Bluming MD book entitled Estrogen Matters (28). We know that no increase was found in BC in the ERT arm of WHI (8) as well as in BC with ET alone in the Million Women Study (18), and in BC in the Nurses' Health study in women on ERT (25). In addition, no increase was found in cancer mortality after 16 years of follow up after WHI (29). Studies showed the efficacy of ET therapy in treating BC (30). The use of progesterone in women receiving E who had maintained their uterus could have theoretically contributed to the lower incidence of IBC (3). Benefits of progesterone/progestins in ER+/PR+ tumors remain controversial (31).

A final limitation of this study is the lack of a matched control group in the study design. This study, similar to the Dayton study, was set up as a "real world" study of women who met the clinical criteria for T deficiency. It was not set up as a controlled pharmaceutical trial. Finally, some may consider a limitation of this study the lack of control for aromatization. The individual and potential synergistic effects of anastrozole with T remain controversial and unknown. Our data was generated and accrued prior to the Dayton experience.

Our 9-year data supports the clinical studies in the literature supporting protective effects of T administration in pre- and post-menopausal women reducing the incidence of BC. Other benefits related to symptom relief of T deficiency have been reported over the past 80 years. Hundreds of thousands of women have seen an improvement in their general health and quality of life by optimizing their hormones. At this point, no FDA approved human identical T is commercially available for women. Our safety data (under review) and this large "real world" observational study hopefully will narrow the gender gap regarding approval of T implant formulations for women.

The Testosterone Therapy and Breast Cancer Incidence Study, a 9-year retrospective study, demonstrated a 35.5% reduction in IBC compared to the age matched SEER expected incidence. The large sample size and length of this trial make it one of the most significant studies on this subject reported to date. Age of patients and other demographic data represents a normal population for study in a general Ob-Gyn practice with neither excess nor diminished risk for IBC. This is the second long-term study in women evaluating the protective effect T subcutaneous hormone implants for IBC.

We should remain cognizant that hormone preparations have changed over the years. Route of delivery matters in assessing risk and side effects. That association does not equal causation. Evidence-based medicine provides the best research evidence and clinical knowledge to assess and treat clinical syndrome and symptoms of the menopause. Finally, improving quality of life in menopausal patients often involves shared decision-making with our patients (32).

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Ethics Committee Approval: This retrospective study was performed with an IRB exemption, Integreview Protocol # 002 (Donovitz).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

G.D. designed the study. Both M.C. and G.D. administered all of the hormone pellet therapy. Both authors contributed to the writing of the manuscript and approved the final manuscript.

Conflict of Interest and Financial Disclosure: G.D. is the Founder, Chairman, and Chief Medical Officer of BioTE Medical, L.L.C. a training and marketing company for instruction in various HRT modalities. M.C. is the owner of the Institute for Hormonal Balance.

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Original Article

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Evaluation of Factors Related to Postoperative Complications in Patients Who Underwent Reduction Mammoplasty

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ABSTRACT

Objective: This study aimed to investigate whether there was an increase in the number of postoperative complications in patients undergoing reduction mammoplasty depending on the technique used (i.e., pedicle type, skin incision pattern), existence of concomitant diseases, and presence of other risk factors.

Materials and Methods: A total of 186 patients who underwent breast reduction between 2013 and 2018 (bilateral, n = 170; unilateral, n = 16) were included in the study. A retrospective review of the data of patients who underwent reduction mammoplasty, which was performed by the same surgical team in a single institution over a 6-year period, was carried out. Superomedial, superior, and inferior pedicles were used in 99, 55, and 32 patients, respectively. The median follow-up period was 4 years.

Results: The median patient age was 45 (range: 16–75) years. The median total reduction weight was 2,194 (range: 80–4,800) grams. The median distance between the sternal notch and nipple was 31 cm (range: 24–45 cm) for the right breast and 30 cm (range: 22–45 cm) for the left breast. The overall complication rate was 6.9%. The complication rates in patients with and without any concomitant diseases were 10.2% and 4.6%, respectively. The overall complication rate was significantly higher in patients with smoking habit, accessory breasts, progesterone use, cerebrovascular disease, morbid obesity (Body Mass Index ≥40 kg/m^2), and thalassemia.

Conclusion: Our analysis shows that the presence of concomitant diseases increases the risk for postoperative complications in patients who underwent reduction mammoplasty. Our findings do not suggest that any of the techniques have significant superiority to each other in terms of pedicle safety and overall complication rate.

Keywords: Breast reduction, superomedial pedicle, superior pedicle; inferior pedicle

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Key Points

- Our analysis shows that the presence of concomitant diseases increases the risk for postoperative complications in patients who underwent reduction mammoplasty.
- Our findings do not suggest that any of the techniques are superior to each other in terms of pedicle safety and risk of overall complications.
- No correlation was found between complications and high blood pressure, excessive breast reduction weights, and long sternal notch-nipple-areola complex distance.

Introduction

Although the main purpose of breast reduction is to reduce weight and volume of the breast, the aesthetic result is equally important. Excellent methods have been identified, and interest has shifted toward technical advancements that provide improved as well as reliable aesthetic results. At the same time, great importance is devoted to the protection of sensory and physiological functions.

Women want to reduce their breasts for both physical and psychological reasons. Heavy, saggy breasts; neck, back, waist, shoulder, and arm pain; and scars on the shoulders due to the compression of bra straps are among their complaints. As pain may become chronic, it may be at risk to maceration and dermatoses in subcutaneous areas. From a psychological aspect, very large breasts could be a focus of serious distress for young women as well as young girls. In unilateral asymmetric hypertrophy, this distress increases further (1).

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Various studies have demonstrated the role of reduction mammoplasty in reducing physical symptoms and increasing quality of life (2-9). Reduction mammoplasty has not only been shown to help resolve these physical symptoms and functional limitations in women, but has also been shown to significantly improve self-confidence and reduce emotional anxiety and depression (10-13). Recent research has shown an improvement in weight loss, exercise/physical activity levels, and even eating behaviors of patients (14). Given these benefits, many women choose to undergo reduction mammoplasty. According to the American Society of Plastic Surgeons, 129,937 breast reductions were performed in 2017. This was done with a number of techniques, involving various pedicles, and skin resection designs.

Studies have shown that the inferior pedicle is the technique preferred by most American plastic surgeons (69%) because it provides vascular reliability (15). However, the superomedial pedicle (SMP) technique is a reliable vascular pedicle method and an important alternative approach for reduction mammoplasty. Studies have also shown that SMP reduction mammoplasty technique is a safe and effective reduction method in cases of mild and moderate hypertrophy.

The superior pedicle technique was first described by Arie in 1957, who found it unreliable because nipple viability is compromised for long pedicle reconstructions (16). This technique was further refined by the inclusion of the medial parenchyma in 1975 by Orlando and Guthrie. They included a medical pedicle that would better provide nipple-areola complex (NAC) vascularity (17). Subsequent studies using this approach have demonstrated its safety in larger breast reductions, and its complication rate was equivalent to that of the inferior pedicle technique. Comparative studies have also demonstrated reduced operative time, better cosmetic durability (less sagging or pseudoptosis over time), and fuller superior and medial appearance (beautiful décolleté) with the SMP technique (18, 19).

In this study, we aimed to present the long-term results of our patients who underwent breast reduction and investigate whether there was an increase in the number of complications in patients undergoing reduction mammoplasty based on the technique used (i.e., pedicle type, skin incision pattern), existence of concomitant diseases, and presence of other risk factors.

Materials and Methods

A total of 186 reduction mammoplasties performed between 2013 and 2018, which were carried out by the same surgical team in a single institution for a 6-year period, were included in this retrospective study. Patient demographic characteristics, preoperative breast measurements, and perioperative data were analyzed. A literature review regarding the complication rates of breast reduction surgery was also performed.

Of the 186 patients with symptomatic breast enlargement, 170 had undergone bilateral and 16 had unilateral reduction mammoplasties. Patients were assessed visually and by the measurement of nipple midclavicular point before surgery, and the procedures were performed by the same team. The superomedial, superior, and inferior pedicles were used in 99, 55, and 32 patients, respectively. The median patient age was 45 (range: 16–75) years. Data were analyzed retrospectively over a 6-year period. The study population was composed of all women aged 16–75 years who had undergone bilateral and unilateral reduction mammoplasty for symptomatic macromastia. The average follow-up duration of the patients was 4 years (range: 2–7 years).

Surgical technique

Markings were made while the patient was standing. The midsternal point, inframammary fold, and meridians of the breasts were marked as a line extending from the nipple to the midclavicular point. A line tangent to the most inferior point of the fold is drawn. The projection of the line was carried to the front of the breast, and the new nipple position was marked on the front of the breast at the level of the inframammary fold. For patients planned to have an inverted t scar pattern, a Wise pattern was drawn with arms of 5–6 cm in length. These lines are further extended medially and laterally until they intersect with the inframammary fold. For patients planned to have a vertical scar, a keyhole pattern is drawn to accommodate the vertical scar.

The pedicle was designed to have an average width of 8–10 cm at the base. The skin over the pedicle except the nipple and areola was de-epithelialized. A dermoglandular excision was performed, and the NAC was transposed into its new location. A thin breast tissue on the muscular structures was preserved in favor of the sensory innervation of the NAC. Medial and lateral pillar sutures were placed, and layered closure of skin incisions was performed. Drains were placed at the end of the surgery.

The three reduction techniques used in breast reduction have not been approached with any bias, and we have successfully applied all of them. Following the measurement of the distance between the sternal notch (Sn) and the NAC (Sn-NAC), we also considered patient's age, height, and comorbidities to decide on the pedicle type. An Sn-NAC distance of >38 cm was usually considered for the inferior pedicle rather than for the SMP. We were inclined to prefer the inferior pedicle and SMP in certain age group (such as >60 years old) instead of the superior pedicle. Although there were no sharp boundaries, we usually chose those who are over 1.65 m in height to be taller than the average population and preferred superomedial and superior pedicle in this group. Comorbidities such as diabetes, smoking, wound healing problems, and other systemic diseases were considered for the pedicle selection.

The SMP technique was the most preferred method because of its versatility and speed, both with the inverted t and vertical scar pattern. In this technique, the most high-risk area of surgery is the circulation of the lateral skin flap. This flap was not left too thin or traumatized during dissection. The technique was easy to teach and apply. This pedicle can be combined with the vertical scar technique. The dissection of the pedicle is almost the same with the vertical technique; the only difference is that at the end of the operation, the skin is made suitable for the breast and excess skin is removed by combining it with vertical technique or a short t scar (1).

Statistical analysis

Chi-square test and descriptive analysis were performed using the GraphPad Prism 7.0 software (GraphPad Software, Inc., La Jolla, CA, USA). Difference with a p-value of <0.05 was considered significant.

Results

The inverted t/Wise pattern incision was used in 171 patients, followed by the vertical pattern incision in 15 patients. The median age was 45 (range: 16–75) years, and the median Body Mass Index (BMI) was 29 (range: 22–41) kg/m^2. Eight patients had a history of breast cancer. Patient morbidities included high blood pressure (n = 21), diabetes (n = 11), psychiatric problems (n = 6), asthma (n = 3), tobacco use (n = 8), and drug use (n = 2) (Tables 1-2, Figures 1-4).

Table 1. Summary of patient information (n = 166)

	All patients (n = 186)		Superomedial pedicle (n = 99)		Superior pedicle (n = 55)		Inferior pedicle (n = 32)	
	Median (SD)	Range	Median (SD)	Range	Median (SD)	Range	Median (SD)	Range
Age (years)	45 (±12.8)	16–75	46 (±12.5)	16–69	45 (±11.5)	15–64	36.5 (±13.9)	32–75
Reduction weight (grams)	2,194 (±805)	80–4,800	2,195 (±749)	640–4,050	2,000 (±1161)	80–4,800	2,200 (±646)	1,600–4,400
Right breast reduction (grams)	1,100 (±404)	80–2,350	1,000 (±385)	400–2,100	1,000 (±597)	80–2,350	1,100 (±319)	800–2,200
Left breast reduction (grams)	1,100 (±386)	200–2,450	1,090 (±363)	400–2,000	1,000 (±572)	200–2,450	1,100 (±329)	800–2,200
Right sternal notch-nipple distance (cm)	31 (±4.2)	24–45	31 (±3.2)	25–40	27 (±9.6)	24–45	30 (±5)	24–43
Left sternal notch-nipple distance (cm)	30 (±4.2)	22–45	31 (±3.2)	22–38	26 (±11.6)	24–45	30 (±5.1)	24–43
Transposed sternal notch-nipple distance	20 (±1.7)	18–30	20 (±1.8)	18–30	20.5 (±11.6)	18–23	20 (±1.1)	18–22

SD: Standard deviation; n: Number

SMP

The median total reduction weight, median right breast reduction weight, and median left breast reduction weight were 2,195 (range: 640–4,050) grams, 1,100 (range: 400–2,100) grams, and 1,090 (range: 400–2,000) grams, respectively. The median preoperative SN-nipple distance was 31 cm (25–40 cm) for the right breast and 31 cm (range: 22–38 cm) for the left breast. The median postoperative SN-nipple distance was 20 cm (range: 18–30 cm) for both breasts (Table 1).

Superior pedicle

The median total reduction weight, median right breast reduction weight, and median left breast reduction weight were 2,000 (range: 80-4,800) grams, 1,000 (range: 80–2,350) grams, and 1,000 (range: 200–2,450) grams, respectively. The median preoperative SN-nipple

Figure 1. Preoperative frontal **(a)**, oblique **(b)**, and lateral **(c)** views of a patient. Five-year postoperative frontal **(a)**, oblique **(b)**, and lateral **(c)** views of the patient following breast reduction with the superomedial pedicle

Figure 2. Preoperative frontal **(a)**, oblique **(b)**, and lateral **(c)** preoperative views of a patient. Three-year postoperative frontal **(a)**, oblique **(b)**, and lateral **(c)** views of the patient following unilateral breast reduction with the superomedial pedicle

Table 2. Concomitant diseases and conditions

	Superomedial	Superior	Inferior	Total	Complication rate	p-value
High blood pressure	14	6	1	21	1 (4.7%)	0.67
Diabetes mellitus	6	5	-	11	1 (9%)	0.77
Smoking	8	-	-	8	2 (25%)	**0.04(*)**
Breast cancer	2	6	-	8	-	0.42
Psychiatric conditions	6	-	-	6	-	0.49
Asthma	1	2	-	3	-	0.63
Accessory breast	2	-	-	2	1 (50%)	**0.01(*)**
Progesterone use	1	-	1	2	1 (50%)	**0.01(*)**
Hyperthyroidism	1	-	1	2	-	0.69
Arrhythmia	1	-	-	1	-	0.78
Gastritis	1	-	-	1	-	0.78
Migraine	1	-	-	1	-	0.78
Ileus	1	-	-	1	-	0.78
Infertility	1	-	-	1	-	0.78
Sleep apnea	1	-	-	1	-	0.78
Ankylosing spondylitis	-	1	-	1	-	0.78
Cyst hydatic	-	1	-	1	-	0.78
Coronary artery disease	-	1	-	1	-	0.78
Multiple sclerosis	-	1	-	1	-	0.78
Scoliosis	-	1	-	1	-	0.78
Cerebrovascular disease	-	1	-	1	1 (100%)	**0.00025(*)**
Morbid obesity (BMI ≥40)	-	1	-	1	1 (100%)	**0.00025(*)**
Thalassemia	-	1	-	1	1 (100%)	**0.00025(*)**
Post bariatric	-	-	1	1	-	**-**
Total number of patients with concomitant diseases	**47**	**27**	**4**	**78**	**8 (10.2%)**	
Total number of patients without concomitant diseases	**52**	**28**	**28**	**108**	**5 (4.6%)**	**0.13**

Significant p-values are shown in bold.
BMI: Body mass index; (*): p<0.05

distance was 27 cm (range: 24–45 cm) for the right breast and 26 cm (range: 24–45 cm) for the left breast. The median postoperative SN-nipple distance was 20.5 cm (range: 18–23 cm) for both breasts (Table 1).

Inferior pedicle

The median total reduction weight, median right breast reduction weight, and median left breast reduction weight were 2,200 (range: 1,600–4,400) grams, 1,100 (range: 800–2,200) grams, and 1,100 (range: 800–2,200) grams, respectively. The median preoperative SN-nipple distance was 30 cm (range: 24–43 cm) for the right breast and 30 cm (range: 24–43 cm) for the left breast. The median postoperative SN-nipple distance was 20 cm (range: 18–22 cm) for both breasts (Table 1).

The overall complication rate was 6.9%. A free nipple graft was needed during surgery for hematoma in three patients, infection occurred in one patient, enlarged scar formation in one patient, wound healing problems in two patients, development of areolar partial necrosis in two patients, and areolar total necrosis in one patient. The complication rates in patients with and without concomitant diseases were 10.2% and 4.6%, respectively (Table 3). These results reveal 2.2 times increase in the risk of complication in patients with concomitant diseases. The overall complication rate was significantly higher in patients with smoking habit (25%, p = 0.04), accessory breast (50%, p = 0.01), progesterone use (50%, p = 0.01), cerebrovascular disease (100%, p = 0.00025), morbid obesity (BMI ≥40 kg/m^2; 100%, p = 0.00025), and thalassemia (100%, p = 0.00025). The overall complication rate was higher in patients with diabetes mellitus (9%, p = 0.77), but this increase was not significant. In addition, no correlation was found between complications and high blood pressure, psychiatric conditions, asthma, hyperthyroidism, arrhythmia, gastritis, migraine, ileus, infertility, sleep apnea, ankylosing spondylitis, cyst hydatic, coronary artery disease, multiple sclerosis, scoliosis, and post bariatric surgery (p>0.05) (Table 2, Figure 5). The median total reduction amount in 13 patients with postoperative complications was

2,600 (range: 462–4,800) grams; compared with the total reduction amount in patients without any complications, the difference was not significant (p = 0.07). The median SN-nipple distance in 13 patients with postoperative complications was 35 cm (range: 24–45 cm); compared with the SN-nipple distance in patients without any complications, the difference was not significant (p = 0.06). The complication rates were 6.06%, 7.2%, and 9.3% for the superomedial, superior, and inferior pedicles, respectively, and the difference was not significant (p>0.05). The risk for partial areolar necrosis was significantly increased in patients with superior pedicled breast reduction (p = 0.02) compared with other pedicle techniques. The risk for nipple contraction/nipple sensory loss was significantly increased in patients with inferior pedicled breast reduction (p = 0.02) compared with other pedicle techniques. No other significant correlation was found between a specific complication and pedicle type.

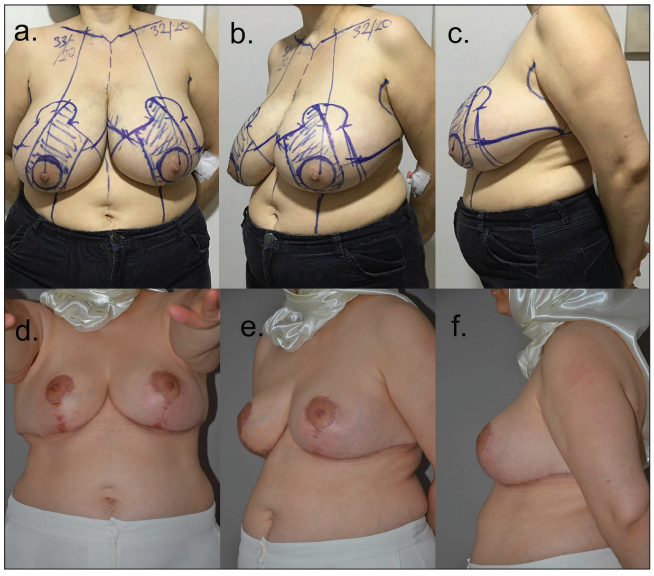

Figure 3. Preoperative frontal **(a)**, oblique **(b)**, and lateral **(c)** views of a patient. Two-month postoperative frontal **(a)**, oblique **(b)**, and lateral **(c)** views of the patient following breast reduction with the superomedial pedicle

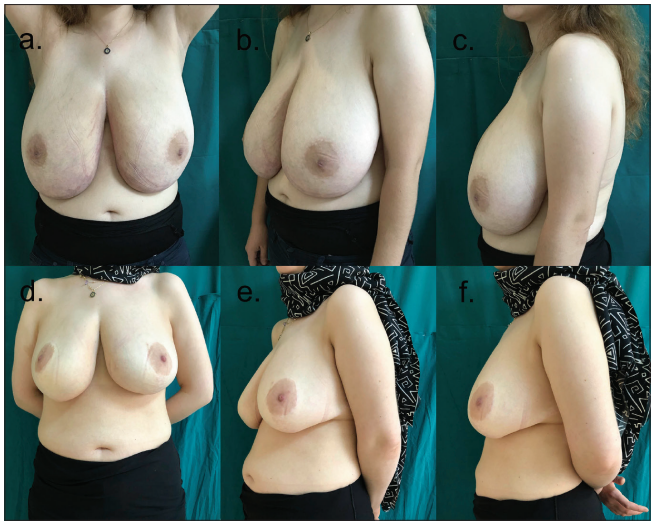

Figure 4. Preoperative frontal **(a)**, oblique **(b)**, and lateral **(c)** views of a patient. Five-year postoperative frontal **(a)**, oblique **(b)**, and lateral **(c)** views of the patient following breast reduction with the inferior pedicle

Complications were properly treated in the clinic by hematoma evacuation, antibiotic therapy, scar revision, necrosis debridement, secondary suturing, and dressing. All patients were followed up for an average of 4 years in terms of wound separation, scar pigmentation, areola and fat necrosis, sensory quality, hypertrophic scar, and keloid. As a result, satisfactory results were achieved in terms of aesthetic appearance over a long-term period. None of the patients had complaints regarding the shape of the breasts. All patients were doing well at the 6th postoperative month, and all of them had gained symptomatic relief after surgery.

Discussion and Conclusion

Prior to breast reduction, surgeons would have chosen a skin incision pattern and a pedicle technique appropriate for the patient's needs. In our clinic, we use both vertical technique and inverted t skin pattern technique depending on the size of the breast, degree of sagging, and patient's wishes. Even in cases where we chose the inverted t technique, we were able to shorten the horizontal scar component, owing to our increasing experience of the vertical technique. That is, when a short transverse scar is added to the vertical technique, or when the traverse scar component in the inverted t technique is shortened, the difference between the vertical and inverted t techniques becomes less obvious (1).

Most American plastic surgeons still use the inferior pedicle and inverted t scar pattern. This technique has many important advantages, as it is primarily reproducible, simple, and easy to teach. Skin incisions are largely compatible with glandular incisions in the breast parenchyma. In this way, after the preoperative drawings were made, all surgical progressive planning such as cutting of tissues and closing of the wound can be completed by following the line markings. This provides a great advantage in terms of predictability and reliability. In contrast, in vertical scar techniques, there is a marked discrepancy between skin incisions and glandular incisions under the skin. To obtain an acceptable result, the amount of tissue to be removed must be well adjusted and tissues must be reshaped during surgery. Finally, it may be necessary to adjust the excess skin

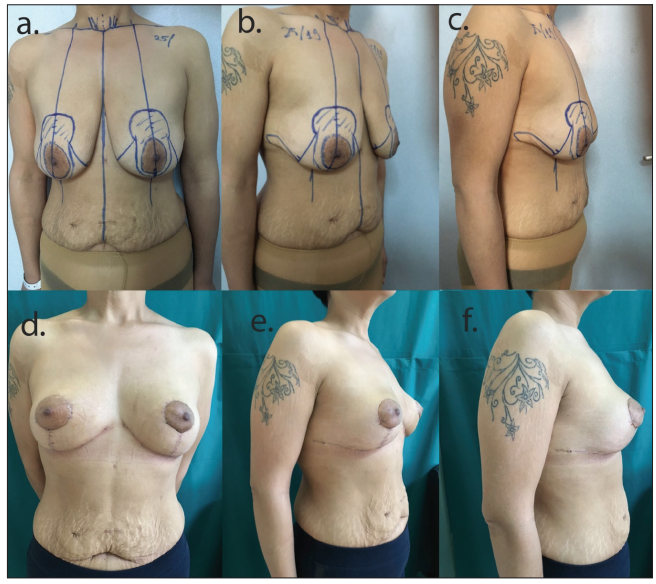

Figure 5. Preoperative frontal **(a)**, oblique **(b)**, and lateral **(c)** views of a patient. One-year postoperative frontal **(a)**, oblique **(b)**, and lateral **(c)** views of the patient following breast reduction with the superior pedicle

Table 3. Complication rates following surgery

	All patients (n = 186)		Superomedial pedicle (n = 99)			Superior pedicle (n = 55)			Inferior pedicle (n = 32)		
	Number	Percentage	Number	Percentage	p-value	Number	Percentage	p-value	Number	Percentage	p-value
Overall complication rate	**13**	**6.9%**	**6**	**6.06%**	**0.59**	**4**	**7.2%**	**0.92**	**3**	**9.3%**	**0.56**
Hematoma followed by free nipple graft	3	1.6%	2	2.02%	0.63	1	1.8%	0.88	-	-	0.42
Infection	1	0.53%	1	1.01%	0.34	-	-	0.51	-	-	0.64
Hypertrophic scar	1	0.53%	1	1.01%	0.34	-	-	0.51	-	-	0.64
Wound dehiscence	2	1.07%	1	1.01%	0.92	-	-	0.35	1	3.1%	0.21
Partial areolar necrosis	2	1.07%	-	-	0.12	2	3.6%	**0.02(*)**	-	-	0.51
Total areolar necrosis	1	0.53%	-	-	0.28	-	-	0.35	1	3.1%	0.21
Fat necrosis	2	1.07%	1	1.01%	0.92	1	1.8%	0.52	-	-	0.51
Nipple contraction/nipple sensory loss	1	0.53%	-	-	0.28	-	-	0.51	1	3.1%	**0.02(*)**
Revision surgery	6	3.22%	4	4.04%	0.50	2	3.6%	0.82	-	-	0.25

Significant values are shown in bold.
n: Number; (*): p<0.05

remaining in the caudal part of the vertical incision when closing the skin (1).

Orlando and Guthrie were the first to describe and present the reliability of SMP techniques. As advantages, the SMP technique maintains the dermoglandular integrity of the NAC. The pedicle can be kept in full thickness and rotated without thinning. This reduces the risk of nipple necrosis, a frightening complication, not only due to the predominant perforator vessels of the internal thoracic artery, but also due to the microvascular connection of the dermal plexus. Other researchers argue that this helps improve the venous drainage of the NAC. Although not evaluated, the duration of surgery tends to be shorter with this technique because much less time is spent during surgery and breast shaping closure can be performed more easily and quickly than other techniques.

The complication rates in our study were lower than those in other published complication rates associated with SMP use (20). Four previous studies have compared the two techniques and provided individual complication rates (20-23). In 17 cases selected from 1987 to 2019, complications related to the superomedial technique were discussed. The mean complication rate ranged from 16.9% to 43% (20). Twenty publications have discussed complications associated with the use of the inferior pedicle technique. The average complication rate ranged from 29.7% to 71% (20).

Our analysis shows that the adoption of less common techniques, such as superomedial reduction mammoplasties, is potentially safe as with the inferior pedicle technique, while providing additional benefits. Numerous studies have drawn attention to maintaining long superomedial fullness, lower tendency to pseudoptosis, and rapid surgery time in long-term breast shape studies (19-21, 24-28).

In previous studies, higher complication risks were found patients with high BMI, excessive tissue resection weight, and long SN-nipple distance (20, 22, 24, 29). In other studies, the complication rate related to the patient's age and tobacco use did not increase (25, 30). Gulcelik et al. (31) reported no difference in the rate of complications in patients with and without breast cancer who underwent breast reduction surgery. They have also found that BMI was the only factor associated with the complication rate. In our study, the overall complication rate was significantly higher in patients with smoking habit, accessory breast, progesterone use, cerebrovascular disease, morbid obesity (BMI ≥40 kg/m^2), and thalassemia. In addition, no correlation was found between complication rates and high blood pressure, excessive breast reduction weights, long SN-NAC distance, and presence of other concomitant diseases (32).

This study has some limitations. The overall complication rate was low, so results might be different in studies with higher number of patients and complications. Since this was a retrospective study, no specific evaluation of the aesthetic appearance was performed. A prospective randomized study could potentially produce more reliable and comparable results in this regard.

In conclusion, our analysis does not suggest that these three techniques have superiority to each other in terms of pedicle safety. Moreover, no significant correlation was found between the overall complication rate and other risk factors. In most cases, we preferred superomedial and superior pedicle reductions. However, some points need to be examined in more detail in future studies. It will be valuable to compare superomedial fullness and aesthetic breast shape obtained in the early period with that in the late period of using other reduction techniques. In addition, nipple sensitivity and lactation should be

demonstrated with objective calculations instead of subjective and theoretical criteria.

Ethics Committee Approval: Since this is a retrospective study there is no ethics committee approval for this study. Patient consents were obtained for the study.

Informed Consent: Informed consents were obtained from all patients prior to the surgery.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: G.T.; Design: G.T., D.A., M.S.; Supervision: G.T., D.A., M.S.; Materials: G.T.; Data Collection or Processing: G.T.; Analysis or Interpretation: D.A., M.S.; Literature Search: G.T.; Writing: D.A., M.S.

Conflict of Interest: The authors declare that they have no conflicts of interest to disclose.

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Original Article

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A Practical, Clinical User-Friendly Format for Breast Ultrasound Report

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ABSTRACT

Objective: Breast ultrasound (BUS) is often performed as an adjunct to mammography in breast cancer screening or for evaluating breast lesions. Our aim was to design a practical and user-friendly format for BUS that could include the details of the Breast Imaging Reporting and Data System.

Materials and Methods: As a team of radiologists and surgeons trained in the management of breast diseases, we gathered and carried out the project in four phases-literature search and collection of present report formats, summarizing key points and preparing the first draft, seeking expert opinion and preparing the final format, and pilot testing-followed by a survey was answered by the research team's radiologists and surgeons.

Results: It produced a list of items to be stated in the BUS report, the final BUS report format, and the pilot format guide. Then, the radiologists used the format in three active ultrasound units in university-affiliated centers, and reports were referred to the surgeons. At the end of the project, the survey showed a high degree of ease of use, clarity, conciseness, comprehensiveness, and well-classified structure of the report format; but radiologists believed that the new organization took more time.

Conclusion: We propose our design as a user-friendly and practical format for BUS reports. It should be used for a longer time and by various ultrasound centers in order to ascertain its benefits.

Keywords: Breast, ultrasonography, breast diseases

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Key Points

- Breast ultrasound is one of the most frequently used modality in breast screening.
- BUS can detect and define lesions and assist both in diagnosis and treatment planning of breast disorders.
- An applied format for BUS report that could be user-friendly for breast care practitioners was designed and tested.

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Introduction

Breast cancer is the most prevalent female cancer and the first cause of death from cancer in women worldwide (1, 2). Breast cancer screening is achieved by clinical breast examination (CBE) and mammography, but under numerous circumstances, breast ultrasound (BUS) is used as a complementary modality (3). Breast complaints are also among the most common causes for women to attend surgery and gynecology clinics (4). In addition to breast examination, many cases need to be further examined by imaging, and BUS is one of the most frequently used modalities in this regard. Also, in many referral centers, breast surgeons regularly use ultrasound imaging as an adjunct to clinical examinations.

BUS can detect and define lesions and assist both in diagnosis and treatment planning of breast disorders, especially in discrimination of solid and cystic masses, which is beyond the diagnostic field of mammography, and in detection of hidden masses in dense breast mammogram. However, in many situations, lesions detected by BUS undergo serial ultrasound to follow the probable changes of that specific lesion [usually Breast Imaging Reporting and Data System (BIRADS) III Category: a probably benign lesions], in order to discriminate benign and suspicious ones.

How to define findings in BUS and which features to note in the report have been described in the ultrasound lexicon and the Breast Imaging Reporting and Data System (5).

A precise BUS report denoting all details is certainly helpful, but two key problems arise. First, which of these details would help the in-charge physicians in medical decision-making and would affect the management plan? Second, how should the arrangement of the report be in order to make it practical and easy to use? In other words, the user of a BUS report is the physician that is managing the breast disorder, who is usually a breast or general surgeon, a gynecologist, or perhaps a family practitioner general physician.

The format of the report, the arrangement of the details, and the number of significant or nonsignificant details affect the practicality and usefulness of the report. A wisely organized report, with the details applied in an orderly manner, would save the clinicians' time and help them figure out the clinically significant points aptly.

In addition, all BUS must be compared with the previous ones in order to identify changes in previous lesions or new findings. At present, various ultrasound units use different formats, although many observe the key problems of the BIRADS system and lexicon. These various styles may make the comparison between ultrasound reports very time-consuming and sometimes ambiguous. A comparison would be simpler if all BUS reports were arranged systematically and uniformly and especially if they were all arranged in the same form.

As a team of radiologists and clinicians whose main field of interest is the management of breast diseases, we have carried out a study to design the applied format for BUS report, which would yield the above advantages.

Materials and Methods

This project was supported by the Vice-Chancellor in Research Affairs of Tehran University University of Medical Sciences and was assessed and ethically approved by its Ethics Committee (ethics code: IR.TUMS.VCR.REC.1 397.846).

We formed a team including radiologists and surgeons who are expert in the management of breast diseases. All radiologists were dedicated to gynecological imaging or breast imaging and have practiced in the radiology departments of Tehran University of Medical Sciences (Tehran), which ranks first in education and research among medical universities of the country. In Iran, as in many other countries, patients undergo ultrasound in different centers on the basis of which they can book an appointment. In addition, radiologists generally mention all the lesions they detect in the BUS in their reports, although unfortunately most clinicians do not mention an individual target lesion to be assessed when they are requesting the BUS. In our country, surgeons are responsible for the clinical management of breast diseases, and surgical oncologists and breast surgical oncologists are trained and entitled for subspecialized practice over the subject. All the surgeons of our research team were surgical oncologists or breast surgical oncologists and practiced as full-time or part-time professors at our university. We performed the study in the following four phases.

Phase 1: Literature search and collection of present report formats

This phase consisted of two stages that were accomplished by one of the surgeons and a research expert. In the first stage, an extended search of the English literature from 1990 to the present time was performed for similar works and different viewpoints about the ultrasound BIRADS lexicon. The rationale for beginning the search from the 1990s was because the first version of BIRADS was issued in 1993 by the American College of Radiology (ACR) (6). The keywords consisted of BUS report, BIRADS ultrasound, BUS interpretation, breast imaging report, and breast mass radiologist assessment. All articles containing relevant data or viewpoints were gathered. Also, chapters or paragraphs about the subject in referral radiology or breast books were investigated in this stage.

In the second stage, we collected BUS reports from high-volume and low-volume radiology centers in Tehran, the capital of Iran, and from several centers in large or small cities around the country. In order to provide a basis for detection of defects of the reports and compare them, we outlined them grossly as four types of formats, which are summarized in Figure 1.

Phase 2: Summarizing key points and preparing the first draft

Two of the surgeons completed this phase in three steps. In the first step, the key points in the BUS report were extracted from the ultrasound BIRADS lexicon and the few related returned articles in our search. In the second step, all collected reports were reviewed and evaluated regarding precision, clarity, and ease to use of the arrangement, as well as ambiguous, vague, or complicated definitions or organization of the items in the second step.

In the third step, the items to be defined in a BUS report were designated according to the BIRADS lexicon; and the most appropriate order for the reporting of those items was argued, in an effort to describe an order which could provide the highest clarity. Several designs were prepared as drafts to be discussed.

Phase 3: Seeking expert opinion and preparing the final format

The third phase consisted of an expert panel, attended by two breast surgeons, three surgical oncologists, eight breast and gynecologic radiologists, and a research expert and then several virtual meetings

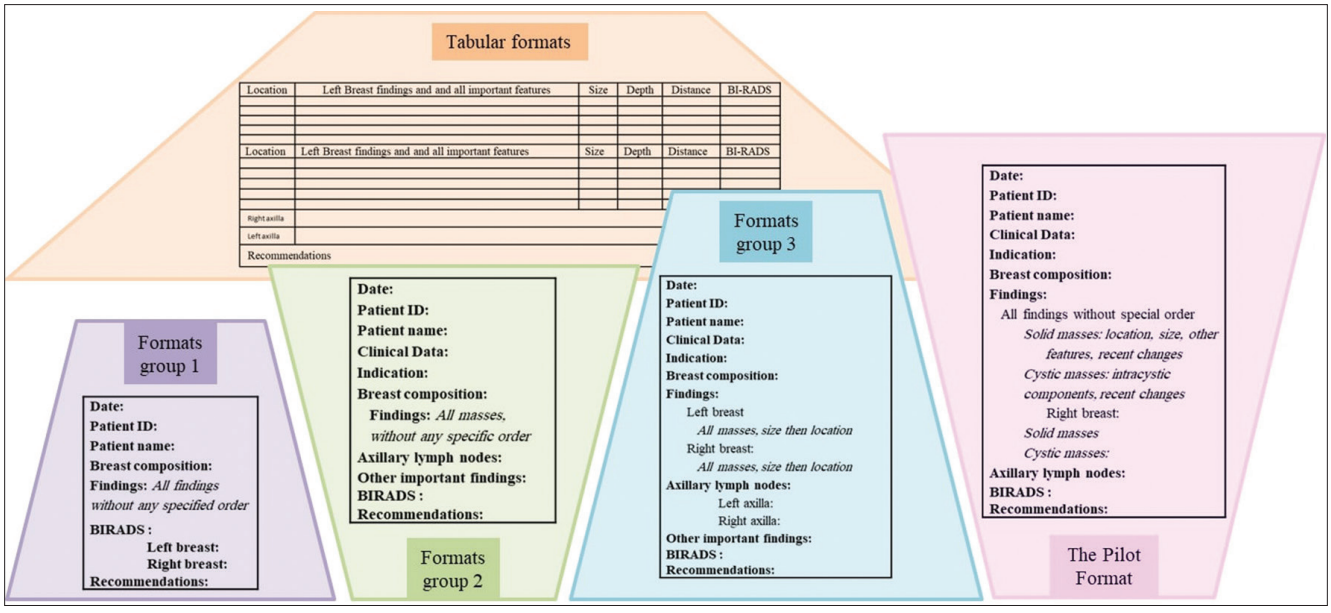

Figure 1. General gross classification of the frameworks of existing breast ultrasound report and comparison with the approved pilot format (all frameworks are shortened to fit in the figure)

ID: Identification; BIRADS: Breast Imaging Reporting and Data System

in the era of coronavirus disease-2019 (COVID-19) through a virtual group including all the named experts as members. The drafted designs for BUS report were introduced and debated during the meetings. One design was designated as most user-friendly, and further modifications were proposed. After several revisions, a final framework was defined and approved as a BUS report pilot format.

Phase 4: Pilot testing

The last phase consisted of pilot testing of the approved format. This was supposed to be uniformly held in ultrasound units of university hospitals for 4 months, so that a comparison of two subsequent results could take place in some cases that underwent two BUS in a 3-month interval. Due to COVID-19 conditions and the delay in many schedules including holding of most screening programs, the number of monthly BUS dropped largely; however, three major units remained active, although with a small number of patients. These were the centers where the radiologists and surgeons of the research team were practicing. Therefore, the pilot was held in these three units for around 5.5 months. After this time, a survey was carried out to assess the format from the point of view of the research team's radiologists and surgeons.

Results

The first product of the panel was the list of items to be stated in the BUS report based on the ultrasound BIRADS lexicon, as demonstrated in Table 1.

The second product was the final BUS report format, which was proposed as a straightforward, user-friendly framework for reporting BUS. Since the format could only demonstrate the basic structure for writing the report, a guideline (the pilot format guide) was also written to explain how and where to describe the items in the framework. Table 2 illustrates the BUS report pilot format, and Table 3 shows the pilot format guide.

Following the establishment of the program in the three units, radiologists' reports were printed according to the proposed format, and the patients brought them to their surgeons according to their schedules.

A brief survey was designed to investigate the impression of the specialists about the new format, and the responses were rated on a 5-point Likert scale: strongly disagree, disagree, undecided, agree, and strongly agree. The survey contained 11 questions, as seen in Table 4. After 5.5 months project execution, all surgeons and radiologists filled the survey. The results of the survey for each group and for all experts are demonstrated in Figure 1 and Figure 2. The average number of BUS performed by each radiologist and seen by each surgeon per month is approximately 200 cases in non-COVID-19 conditions.

Discussion and Conclusion

We performed a study to design and test an applied format for BUS report that could be user-friendly for breast care practitioners. After gathering the existing formats and assessing them, we defined a framework and its user guide through several panels and tested it in three high-volume BUS units, with favorable outcomes.

The sensitivity of mammography in detecting suspicious lesions is variable and is overall lower in dense breast tissue (3, 7, 8). Adding BUS to mammography increases the sensitivity for detection of breast cancer in women with high mammographic breast tissue density (9). Berg et al. (10) performed a multicenter study involving 2809 women at high risk for breast cancer to find out if the inclusion of BUS to mammography may have an effect in the diagnostic yield of the latter during breast cancer screening. They showed a diagnostic yield of 7.6 versus 11.8 per 1,000 women screened for mammography alone and the combination of the two modalities, respectively (2). Gharekhanloo et al. (11) also confirmed the additional sensitivity provided by adding BUS to mammography for the detection of breast cancer in their study on 300 cases. The additional advantage of BUS in mammographic

Table 1. Items to be stated in the BUS report as approved in the expert panel

General items	
History	Previous breast medical and surgical history or previous biopsy results
Family history	Of breast cancer
Indication	For performing the BUS
Breast composition	Homogenous background echotexture-fat/homogenous background echotexture-fibroglandular/ heterogenous background echotexture
Findings	
Mass	Described as below
Tissue distortion	Described as below
Retraction	Described as below
Calcification	Described as below
Lymphadenopathies	Location (axillary, in breast), significance, cortical thickness, hilum changes, extracapsular invasion, matted nodes
Skin changes	Edema, thickness, retraction
Nipple changes	Retraction
Postoperative findings	
Descriptions for any breast finding	
Side	Left/right
Location	On a clock face
Distance (mm)	From the nipple
Depth (mm)	From the skin
Comparison	Comparison with previous ultrasound examination
Descriptions for masses	
Size (mm)	The largest dimension or the three dimensions
Type	Cystic, solid
Echopattern	Anechoic, hypoechoic, isoechoic, hyperechoic, heteroechoic
Shape	Round, oval, irregular
Lobulations	Microlobulations, macrolobulations; number
Margins	Circumscribed, indistinct, angular, spiculated
Orientation	Horizontal, vertical
Posterior features	None, enhancement, shadowing, combined pattern
Vascularity	Absent, internal, vessels in rim
Elasticity	Soft, intermediate, hard
Intracystic details	Septations, masses
Postoperative findings	
Significant recent change in findings	
Correlation with mammographic, MRI, or clinical findings	
BIRADS	
Recommendations of the sonographer	

BUS: Breast ultrasound; BIRADS: Breast Imaging Reporting and Data System; MRI: Magnetic resonance imaging

breast cancer screening in women at high risk of breast cancer has been maintained by the American College of Radiology Imaging Network via a multicenter trial (12).

In addition to screening purposes, BUS assists in the evaluation of breast symptoms and signs, including lumps or nipple discharge. In many instances, lesions that appear benign need to be followed regarding their shape, size, or other features; a part of the follow-up is performed by serial BUS. Hence, overall, BUS plays a significant role in the approach to the breast.

In 2003, the ACR released a BIRADS lexicon for ultrasound that intended to standardize BUS reports and simplify comparisons with previous imaging (5). This has yielded a kind of international shared

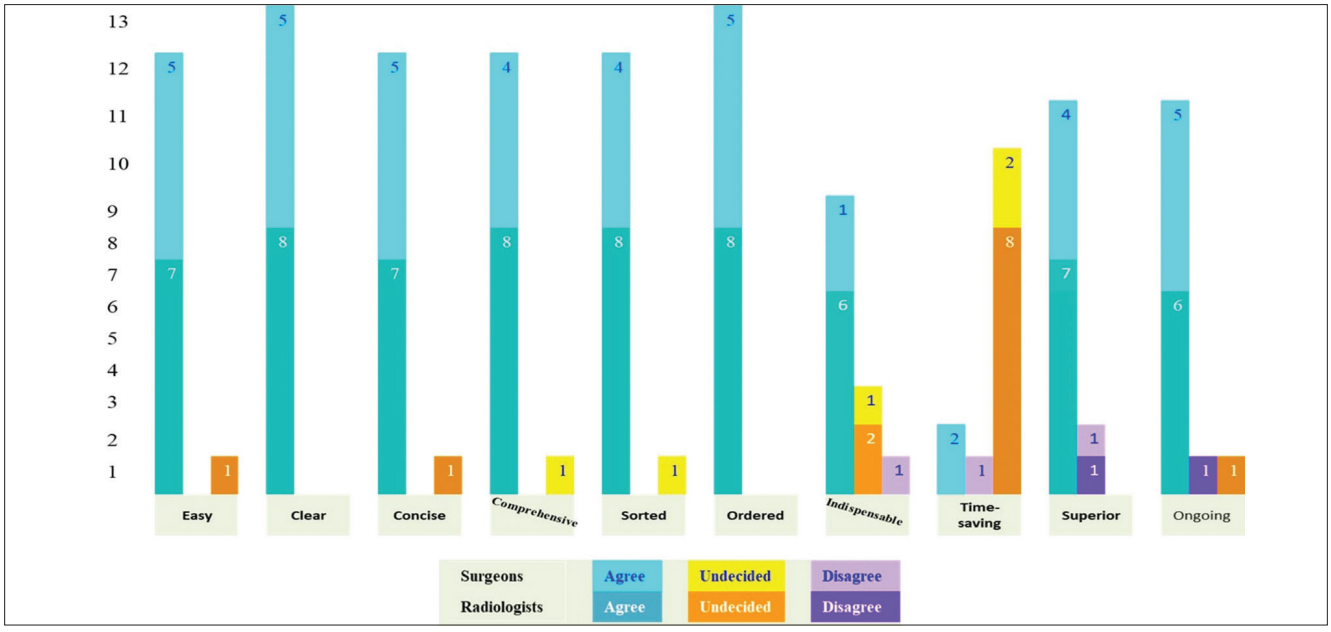

Figure 2. Results of survey among radiologists and surgeons

Table 2. Framework of approved pilot format

- Date:
- Patient ID:
- Patient name:
- Clinical data:
- Indication:
- Breast composition:
- Findings:

♣ Left breast

➢ Solid masses

■

➢ Cystic masses

■

♣ Right breast:

➢ Solid masses

■

➢ Cystic masses:

■

- Axillary lymph nodes:

○ Left axilla:

■

○ Right axilla:

■

- Other important findings:

○

- BIRADS:

○ Left breast:

○ Right breast:

- Recommendations:

ID: Identification; BIRADS: Breast Imaging Reporting and Data System

language between radiologists. Abdullah et al. (13) evaluated the concordance of definitions of five sonographists about ultrasound characteristics of 267 benign and malignant breast lumps based on the BIRADS lexicon for BUS. They detected an overall "good" level of agreement but a fair one for evaluating lesion borders. The concordance of their description was lower for smaller lumps as well as malignant cases. Their overall conclusion was in favor of a good interobserver agreement. This was confirmed by the studies of Lazarus et al. (14) and Costantini et al. (15) on 91 and 178 breast lesions, respectively.

While BUS is performed by radiologists, the clinician has to decide on the suitable approach to a breast lesion based on the findings of breast exam and breast imaging. Consequently, the BIRADS system and the lexicon also aim to ease the communication between the sonographer and the clinician. As a creditable product should be produced by the cooperation of stakeholders with diverse viewpoints from different aspects, several medical organizations have cooperated in the production of the BIRADS lexicon, including associations of surgeons, who could be seen as the end-users of the lexicon product, or the BUS report (16). Items that should be mentioned in a report, descriptors for every item, and the gross order of the report are explained in the BIRADS lexicon for BUS. However, the order of the details, the scope and number of details, and the visual method for emphasizing on more important findings can also be outlined, giving rise to user-friendly reports that could easily be compared. This is what our team aimed for, by delineating an orderly structure for the BUS report, where details appear in accord with the BIRADS lexicon, and the usual classifications of breast lesions. In our proposed format, sorting the lesions by type allows users to selectively pick up the parts they are concerned about or first pay attention to components that are more important to them. By writing the clockface location of each lesion first, the users localize the lesion in their mind and match it with the CBE or other imaging modalities. The size of each lesion immediately follows, because size change is almost the most important alteration that can affect the significance of a finding. Then, the other location coordinates including depth from the skin and distance from the nipple depicted as near zone, mid zone, and far zone are described

Table 3. Guide for approved pilot format

- Date:
- Patient ID:
- Patient name:
- Clinical data (age, history, family history)
- Indication (cause for requesting ultrasound)
- Tissue composition (according to ACR format: homogenous background echotexture-fat/homogenous background echotexture-fibroglandular/heterogenous background echotexture)

Findings:

☛ For suspicious lesions: please write in BOLD + mention ZONE (near zone, mid zone, far zone) and DEPTH (anterior zone, mid zone, posterior zone) + write the BIRADS of that specific lesion

☛ For new lesions or lesions with recent changes, please write in BOLD

☛ For lesions in location of clinician interest, please write in BOLD

☛ For any suspicious finding in the breast other than masses, like tissue distortion or retraction, please write it next to the mass or in the relevant location among masses

☛ If typical, please write the probable diagnosis of the mass (probably fibroadenoma, fat necrosis, hamartoma, intramammary lymph node…)

☛ For any significant finding, if correlated with mammographic, MRI, or clinical findings, please mention it, with BIRADS

☛ Please follow this order:

♣ Left breast:

➢ Solid masses

■ In order of clock hours, first retroareolar, then 1 to 12

✋ In each line, please first write the location (…. O'clock) and the size, then if needed the zone (NZ, MZ, FZ) and the depth (….mm from skin), then the features of the mass as needed (irregular margin, orientation, posterior features, vascularity, elasticity, …)

➢ Cystic masses

■ In order of clock hours, first retroareolar, then 1 to 12

☞ Please only mention BIRADS 3 and 4 cysts, those in region of relevant findings in other imagings, and those in region of clinician interest as requested in their order.

☞ Multiple cystic lesions may be defined in a row.

☞ In each line, please first write the location (…. O'clock), then if needed the zone (NZ, MZ, or FZ) and the depth (…mm from skin), then the features as needed (intracystic mass, septations …).

♣ Right breast:

■ As above

- Axillary lymph nodes:

✎ For normal or reactive lymph nodes please only mention nonsignificance, and do not mention size and other features

✎ Please mention when lymph nodes are relevant to a clinical or other imaging finding

✎ For suspicious nodes, please mention features as needed (cortical thickness, hilum changes, extracapsular invasion, matted nodes, etc.), the BIRADS of that specific lymph node and the recommendation (short-term follow-up, tissue diagnosis…)

- Other important findings (skin changes, duct changes, seroma, etc.)
- BIRADS

Recommendations (follow-up/further imaging/suggestion of tissue diagnosis, etc. for breast or axillary lesions)

✎ Please do not mention type of surgical management

ID: Identification; ACR: American College of Radiology; BIRADS: Breast Imaging Reporting and Data System

in order to ascertain the site of the lesion and a correct comparison with the previous BUS.

After using the format, the survey showed a high level of agreement of the team members with ease of use, clarity, conciseness, comprehensiveness, and well-classified structure. However, radiologists believed that the organization of the report took more time. This could be permanently true or may be temporary due to the novelty of the structure, which might take time to get used to by the radiologists and their assistants who are preparing the report. Two of the surgeons thought the format was time-consuming, and one could not decide about the time; these were considering the time for preparing the

Table 4. Survey questions

Number	Abbreviation*	Question
1	Easy	The format is easy to use
2	Clear	The definitions are clear
3	Concise	The format is concise and useful
4	Comprehensive	The format contains all key elements
5	Sorted	The format contains necessary classifications
6	Ordered	The arrangement is appropriate for comparison of two BUSRs
7	Indispensable	The present details cannot be deleted
8	Time-saving	Using this format takes less time
9	Superior	The format increases the quality of the BUSR
10	Ongoing	I am eager to use the format in all my BUSRs
11**	---------	I will take part in similar studies

*Abbreviations demonstrating the subject of each question in calculations and in the figures, ** Question number 11 is not depicted in the figure because it had no direct relation with the format assessment.
BUSR: Breast ultrasound report

report; the two other surgeons agreed that in comparison with the BUS reports they were receiving before the study, this one took much less time to read, understand, and specially compare with the previous report. The indispensability of all details and whether the report could be further shortened were also questionable for some of the members.

Our study had some limitations. First and foremost, the COVID-19 situation disrupted the usual flow of patients and BUS. In addition, the users of the format were the same as the designers. Therefore, the study should also be performed by other users in other centers provide a more valid assessment of the proposed format.

In conclusion, we propose our format as a user-friendly format for BUS reports, which may be used and introduced as an adjunct to the BIRADS ultrasound lexicon. The format should be applied for a longer time in university hospitals in order to find out if the apparent time-consuming nature for radiologists would be solved by routine use. Also, the format should be tested in other centers in order to ascertain its positive features.

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Original Article

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Prevalence of Incidental Gynecomastia by Chest Computed Tomography in Patients with a Prediagnosis of COVID-19 Pneumonia

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ABSTRACT

Objective: In this study, we aimed to determine the prevalence of gynecomastia by evaluating computed tomography (CT) images of male patients who were admitted to our hospital during the coronavirus disease-2019 (COVID-19) pandemic.

Materials and Methods: This study included a total of 1,877 patients who underwent chest CT for prediagnosis of COVID-19 pneumonia between March 15th and May 15th, 2020. All images were evaluated for the presence of gynecomastia. Gynecomastia patterns were evaluated according to morphological features, and diagnoses were made by measuring the largest glandular tissue diameter. Statistical analysis was performed with IBM SPSS software version 25.0.

Results: The prevalence of gynecomastia was 32.3%. In terms of pattern, 22% were nodular, 57% were dendritic, and 21% were diffuse glandular gynecomastia. A significant correlation was found between age and gynecomastia pattern ($p<0.001$). The incidence of nodular, dendritic, and diffuse glandular gynecomastia increased with advancing age. A significant difference was found in the analysis of the correlation between age groups and glandular tissue diameters ($p<0.001$). With an increase in glandular tissue diameter, the gynecomastia pattern changed from a nodular to a diffuse glandular pattern.

Conclusion: In our study, gynecomastia diagnosis was made through axial CT images. Although CT should not replace mammography and ultrasonography for clinical diagnosis of gynecomastia, chest CT scans can be used to evaluate patients with suspected gynecomastia.

Keywords: Male breast, gynecomastia, CT, nodular pattern, dendritic pattern, diffuse glandular pattern, COVID-19

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Key Points

- The most common benign breast lesion in men is gynecomastia.
- Gynecomastia is a benign enlargement of male breast tissue resulting from an imbalance of estrogen and testosterone levels.
- Gynecomastia may be physiological or idiopathic or caused by concomitant systemic disease or hormone use.
- If gynecomastia is detected with computed tomography, the patient should be evaluated clinically.

Introduction

The normal male breast consists mainly of adipose tissues and several subareolar ductal structures located on the pectoral muscle. Owing to these anatomical features, male breast diseases differ from female breast diseases in terms of frequency and radiological findings (1). Lobule formation is not usually seen during male breast development (1, 2). Fibroadenoma, cyst, and lobular carcinoma of lobular origin are extremely rare pathologies of male breasts (2). Invasive ductal carcinoma, ductal carcinoma in situ, and papillary neoplasm, which are related to ductal and stromal proliferation, as in gynecomastia, occur in men (2).

Benign breast lesions found in men include infection, abscess, tuberculosis, fibrocystic changes, hematoma, lipoma, sebaceous cyst, ductal ectasia, and diabetic mastopathy, but the most common benign breast lesion in men is gynecomastia (1, 3). Gynecomastia can be defined as the development of fibroepithelial structures in the male breast, giving it an appearance similar to healthy female breast. Glandular tissue of ≥2 cm in the subareolar area is generally accepted as gynecomastia (4-7).

The reported prevalence of gynecomastia ranges between 32% and 65% (4). Gynecomastia may be physiological or idiopathic or caused by concomitant systemic disease or hormone use (4, 6). Physiological gynecomastia occurs during the neonatal period, puberty, and old age

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(6). Neonatal gynecomastia is caused by estrogen from the mother. In puberty, nearly half of boys have temporary gynecomastia (6). In other cases, gynecomastia is often idiopathic, where the cause is unclear. Gynecomastia is caused by the imbalance between estrogen and testosterone levels (3, 8).

Gynecomastia has three characteristic patterns: nodular, dendritic, and diffuse fibroglandular (2, 8). On mammographic evaluation, nodular gynecomastia has a fan-like appearance extending from the nipple to the back. If nodular gynecomastia is correlated with a pathological classification, the early phase is called gynecomastia, but this stage is reversible. Dendritic gynecomastia appears as retroareolar soft tissue density with radial extension to deep fatty tissues. It is the equivalent of fibrous gynecomastia in pathological classification. Diffuse glandular gynecomastia appears similar to the female breast. Nodular and dendritic forms can occur together. This is especially common in male patients receiving estrogen. In terms of pathological classification, it corresponds to proliferative epithelial changes accompanied by lobule formation in some cases (1).

The diagnosis of gynecomastia is important for patients to know that they do not have a malignant lesion and, if the cause of gynecomastia is found, to plan treatment (2). In patients presenting with complaints such as breast tenderness, swelling, and mass, ultrasonography (US) is used to diagnose young patients, and mammography is used in older and young patients, if necessary (1). Differential diagnosis of gynecomastia includes malignant tumors. In some cases, gynecomastia and malignancy cannot be easily differentiated. If gynecomastia is detected with computed tomography (CT), the patient should be evaluated clinically and imaged with mammography, if necessary. Pseudogynecomastia, another reason for an increase in breast tissue, is also included in the differential diagnosis of gynecomastia. It is caused by benign diffuse proliferation of adipose tissue (adipomastia) and is seen in overweight or obese people. Generally, pseudogynecomastia can be distinguished from gynecomastia based on the absence of a palpable, suspicious lesion under the areola upon clinical examination; if required, it can also be evaluated by US and mammography (2, 9).

Gynecomastia treatment is evaluated by age group. Hormonal imbalance should be investigated in the adolescent period; usually, gynecomastia regresses spontaneously during adolescence. In a patient with an established cause, discontinuing the drug that causes gynecomastia or treating the underlying medical condition typically results in regression unless the process reaches the irreversible fibrotic phase. Androgens, selective estrogen-receptor modulators, and aromatase inhibitors may provide some benefits for patients whose disease is secondary to other hormonal or medical treatments (9). Reduction mammoplasty can be performed in cases where drug treatment is not appropriate, or if patients are not responsive to other treatments (9).

The rate of gynecomastia in the general population is unknown because most cases are asymptomatic and routine breast imaging is not performed in men. Gynecomastia is a common incidental finding in chest CT (4). However, the prevalence of gynecomastia in Turkey by CT has not been reported.

During the coronavirus disease-2019 (COVID-19) pandemic, chest CT, CT angiography, and high-resolution CT (HRCT) examinations were performed in a large number of patients admitted to our hospital with a preliminary diagnosis of viral pneumonia. In this study, we aimed to evaluate the breast tissue and determine the prevalence of gynecomastia in male patients who were admitted to our hospital and had a chest CT for prediagnosis of COVID-19.

Materials and Methods

This retrospective study was approved by our institutional ethics committee (approval no: 20-8.1T/40) and the Republic of Turkey Ministry of Health, COVID-19 Scientific Research Committee. A total of 4,047 chest CTs were performed in our hospital between March 15th and May 15th, 2020, for preliminary diagnosis of COVID-19 pneumonia. Our study included a total of 1,877 male patients. The mean age was 51.28 years, which ranged from 10 to 95 years (Table 1). Female cases were excluded from the study.

Of the total 1,877 CTs, 1659 (88.3%) were HRCT, 175 (9.3%) were CT angiography, and 43 (2.2%) were non-contrast-enhanced chest CT. Images were taken using a 160-slice CT scanner (Aquilion Prime, Toshiba Medical Systems). Axial images were acquired craniocaudally at shallow inspiration from the thoracic inlet to the diaphragm. HRCT images were taken at a high-resolution CT protocol with 120 kVp, 100–200 mA, and 80 mm × 0.5 mm collimation and reconstructed at 0.5 mm slice thickness with a sharp reconstruction kernel. Chest CTs were performed at a CT protocol with 120 kVp, 100–200 mA, 80 mm × 0.5 mm collimation and reconstructed at 1-mm slice thickness. Chest CT angiography was performed using a CT angiography protocol with 120 kVp, 100–200 mA, and 80 mm × 0.5 mm collimation and reconstructed at 1-mm slice thickness. A bolus of 1 mL/kg body weight of nonionic contrast material (Iopromide, Ultravist 370, Bayer Schering Pharma, Berlin, Germany) was injected intravenously in the antecubital vein at the rate of 4 mL/s by using an automatic injector. The bolus-tracking method was used to optimize pulmonary artery opacification. After termination of contrast agent administration, 50 ml of saline was injected. Diagnoses were determined by using the Sectra IDS-7 program.

All CT images were evaluated for the presence or absence of gynecomastia by a board-certificated radiologist with 14 years of experience. Cases with glandular tissue diameter of ≥2 cm at the nipple level in the axial plane were diagnosed as gynecomastia (Figure 1). When the axial diameter of the glandular tissue was 1-2 cm with a vertical growth and demonstrated characteristics that were consistent with gynecomastia, cases were also diagnosed as gynecomastia (Figure 2). In contrast, cases with glandular tissue diameter of 1-2 cm, but with atretic tissue pattern and density, were considered normal.

Gynecomastia patterns and axial diameter measurements were made separately for the right and left breasts. Gynecomastia pattern was evaluated as nodular, dendritic, or diffuse glandular gynecomastia (Figure 3). Nodular gynecomastia has a fan-like appearance, extending from the nipple to the posterior. Dendritic gynecomastia appears as retroareolar soft tissue density with radial extension to deep fatty tissues. Diffuse glandular gynecomastia appears similar to the female breast. At the same time, the presence of adipomastia was evaluated. In this study, adipomastia was defined as adipose tissue thickness of ≥2.5 cm in the breast tissue at the nipple level in the vertical plane. The presence of chronic diseases such as malignancies, liver cirrhosis, and chronic kidney failure were evaluated from CT images and clinical information records.

Table 1. Distribution of cases according to age and gynecomastia pattern

Age (years)	Gynecomastia pattern				No Gynecomastia	Total
	Nodular	Dendritic	Diffuse glandular	Total		
10–19	5	7	3	15 (1%)	18 (1%)	33 (2%)
20–29	16	47	11	74 (4%)	171 (9%)	245 (13%)
30–39	49	58	13	120 (6%)	215 (12%)	335 (18%)
40–49	17	49	6	72 (4%)	212 (11%)	284 (15%)
50–59	13	56	22	91 (5%)	211 (11%)	302 (16%)
60–69	16	52	23	91 (5%)	194 (10%)	285 (15%)
70–79	14	53	31	98 (5%)	162 (9%)	260 (14%)
80–89	4	22	12	38 (2%)	83 (4.5%)	121 (6.5%)
90–95	1	3	3	7 (0.3%)	5 (0.2%)	12 (0.5%)
Total	135	347	124	606 (32.3%)	1,271 (67.7%)	1,877 (100%)

Values are expressed as n (%).
n: Number

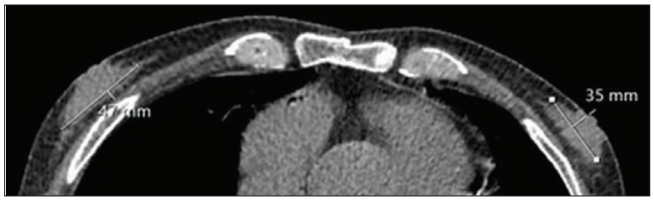


Figure 1. Computed tomography (CT) images showing axial diameter measurement of an 81-year-old patient with bilateral gynecomastia

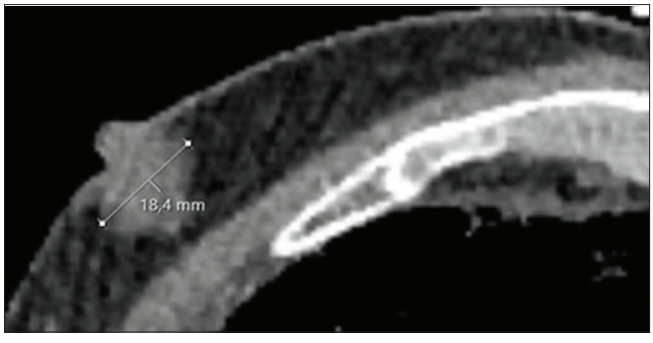


Figure 2. Computed tomography images showing vertical growth of glandular tissue density with an axial diameter of 1–2 cm

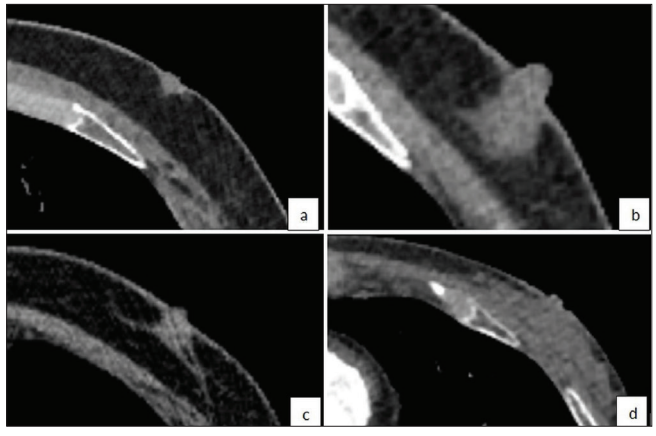


Figure 3. CT images showing patterns of gynecomastia in the male breast. Examples of non-gynecomastic normal retroareolar area **(a)**, nodular pattern **(b)**, dendritic pattern **(c)**, and diffuse glandular pattern **(d)** of gynecomastia

CT: Computed tomography

Statistical analysis

The distribution of cases in age groups, separated by decade, was determined. Continuous data were expressed as mean and standard deviation, and categorical data were expressed as counts (n) and percentages (%). All statistical analyses were performed with SPSS software version 25.0 (IBM). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess normal distribution of data. Pearson's chi-square and Fisher's exact tests were employed to compare gynecomastia patterns and age. Student's t-test was utilized to compare differences of continuous variables in independent groups. Spearman's correlations were used to evaluate the relationship between gynecomastia patterns and breast glandular measurements.

Results

Gynecomastia was detected in 606 (32.3%) of the 1,877 patients, and of those 606 gynecomastia cases, 454 (74.9%) were bilateral and 152 (25.1%) were unilateral (Table 2). Out of the 152 unilateral gynecomastia cases, 75 were observed on the right side and 77 on the left side. Of the 606 gynecomastia cases, 22% had nodular pattern, 57% had dendritic pattern, and 21% had diffuse glandular pattern (Table 1-2). Adipomastia was detected in 84 (4.5%) of 1877 patients.

In cases with axial diameter measurements of 1–2 cm and considered gynecomastia, the enlargement of the glandular density was evident

in the vertical plane. Of the glandular tissue diameter measurements performed in the axial plane of the right breast, 398 (75.3%) cases had a diameter of ≥2 cm and 131 (24.7%) cases had a diameter of 1–2 cm (Table 3). Of the glandular tissue diameter measurements performed in the axial plane of the left breast, 374 cases (70.4%) had a diameter of ≥2 cm; however, 157 cases (29.6%) had a diameter that was 1–2 cm (Table 3).

No significant difference was found in age between the groups with and without gynecomastia (p = 0.495) or between groups with unilateral and bilateral gynecomastia p = 0.674). A significant correlation was found between age groups by decade and gynecomastia patterns with Kruskal-Wallis and Dunn's tests (p<0.001) (Figure 4). As age advanced, an increase was seen trending from nodular pattern to diffuse glandular pattern.

When gynecomastia patterns were compared according to age group, significant differences were found between nodular and dendritic (p = 0.002), nodular and diffuse glandular (p<0.001), and dendritic and diffuse glandular gynecomastia patterns (p = 0.003) with chi-square tests (Figure 5). Nodular, dendritic, and diffuse glandular patterns increased with advancing age.

Kruskal-Wallis tests indicated a significant difference in the correlation between age group and glandular tissue diameter for the right breast (p = 0.004) and left breast (p = 0.006) (Figure 6). Spearman's rho nonparametric correlation test revealed a positive relationship between age and glandular tissue diameter (p<0.001; r = 0.235).

Gynecomastia cases were divided into two tissue diameter groups: 1-2 cm and >2 cm. The relationship between these two groups was determined according to the tissue diameter and age by independent samples Kruskal-Wallis tests. When evaluated with paired comparisons, a significant difference was found between age and tissue diameter for the right breast (p = 0.018) and left breast (p = 0.012). Tissue diameter increased in direct proportion with increasing age.

A significant difference was found between glandular tissue diameter and gynecomastia patterns in the chi-square test for the right breast (p<0.001) and left breast (p<0.001). With an increase in glandular

Table 2. Gynecomastia pattern distribution

Gynecomastia pattern	Bilateral	Unilateral	Total
Nodular	84	51	135 (22%)
Dendritic	251	96	347 (57%)
Diffuse glandular	119	5	124 (21%)
Total	454 (75%)	152 (25%)	606

Values are expressed as n (%).
n: Number

Table 3. Glandular tissue diameter of the right and left breasts

Glandular tissue diameter	Right breast	Left breast
1–2 cm	131 (24.8%)	157 (29.6%)
>2 cm	398 (75.2%)	374 (70.4%)
Total	529	531

Values are expressed as n (%).
n: Number

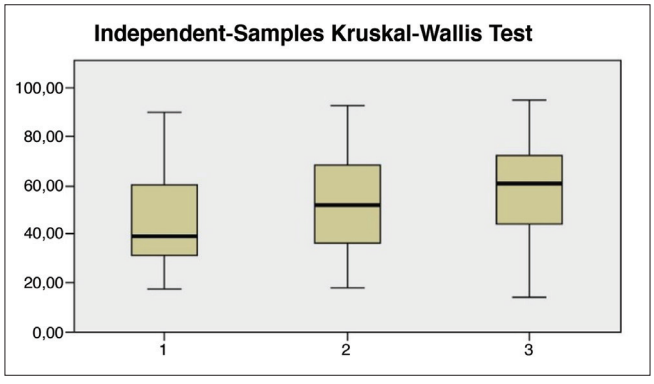
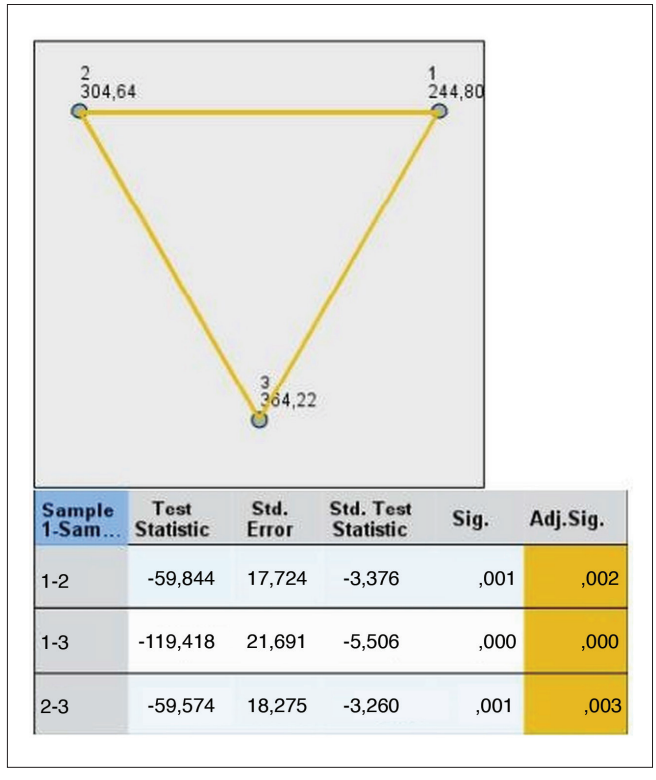


Figure 4. Distribution of age according to gynecomastia pattern (1, nodular pattern; 2, dendritic pattern; 3, diffuse glandular pattern)



Sample 1-Sam...	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj.Sig.
1-2	-59,844	17,724	-3,376	,001	,002
1-3	-119,418	21,691	-5,506	,000	,000
2-3	-59,574	18,275	-3,260	,001	,003

Figure 5. Pairwise comparisons of gynecomastia pattern (1, nodular pattern; 2, dendritic pattern; 3, diffuse glandular pattern)

Std: Standard; Sig: Significance; Adj Sig: Adjusted significance

tissue diameter, the gynecomastia pattern changed from nodular pattern to diffuse glandular pattern. Nonparametric Spearman's rho correlation test indicated a strong positive correlation between both breast glandular tissue diameters and age groups, and this relationship was significant (p<0.001) (Table 4).

Discussion and Conclusion

Male and female breasts are structurally the same until adolescence. During puberty, lobular proliferation occurs following dilatation and branching of the ducts in the female breast. In contrast, usually, no changes occur in the male breast.

Gynecomastia is the most common pathology in the male breast and a common incidental finding in chest CT (3). However, the prevalence of gynecomastia with CT has not been reported in previous studies in Turkey. In this study, the prevalence of gynecomastia by CT images was 32.3%. Breast screening in men is not routinely performed. In symptomatic gynecomastia cases, US and mammography are the preferred imaging methods. Although CT is not superior to mammography in the evaluation of gynecomastia, it may help diagnose asymptomatic cases if reported by radiologists.

Gynecomastia occurs as a result of benign proliferation of ductal and stromal tissues and can be unilateral or bilateral (9). It is caused by the imbalance of testosterone and estrogen levels (3, 8). Other causes include hormone-secreting tumors, endocrine disorders, liver cirrhosis, obesity, drug use, and drug addiction (3, 10). Approximately 20% of gynecomastia cases are caused by drug side effects, but definitive causes are often not detected (10).

Physiological gynecomastia is caused by normal changes in the balance of hormones. Gynecomastia prevalence is 75% in the neonatal period and 50% in adolescent boys, but it usually regresses within 6 months. Gynecomastia peaks during the neonatal period, adolescence, and old age (4, 6). Between these ages, gynecomastia is usually pathological and depends on various diseases, syndromes, drug treatments, or conditions that cause impaired balance of estrogen and testosterone levels (2, 4, 8).

Gynecomastia is found in about half of older men and is usually asymptomatic (2). A study reported a rise in the prevalence of gynecomastia with increased Body Mass Index (4). Gynecomastia is more common in older obese men owing to increased estrogen levels from peripheral adipose tissue and decreased testosterone due to decreased testicular function (6). Previous studies in elderly men have reported gynecomastia in 55% of autopsies, 57% in healthy cases, and 70% in hospitalized patients (11, 12).

Of the cases in our study, 48% were <50 years old, and 52% were ≥50 years old (Table 1). In our study, no significant difference was noted between groups with and without gynecomastia in terms of age (p = 0.495). Considering the distribution of our cases according to age

Table 4. Glandular tissue diameters and age group statistics of nonparametric correlations

Correlations			Age	Right breast glandular tissue diameter	Left breast glandular tissue diameter
Spearman's rho	Age	Correlation coefficient	1	0.235*	0.219*
		p-value	-	<0.001	<0.001
		n	1,877	529	531
	Right breast glandular tissue diameter	Correlation coefficient	0.235*	1	0.769*
		p-value	<0.001	-	<0.001
		n	529	529	454
	Left breast glandular tissue diameter	Correlation coefficient	0.219*	0.769*	1
		p-value	<0.001	<0.001	-
		n	531	454	531

*Correlation is significant at the 0.01 level (2-tailed).
n: Number

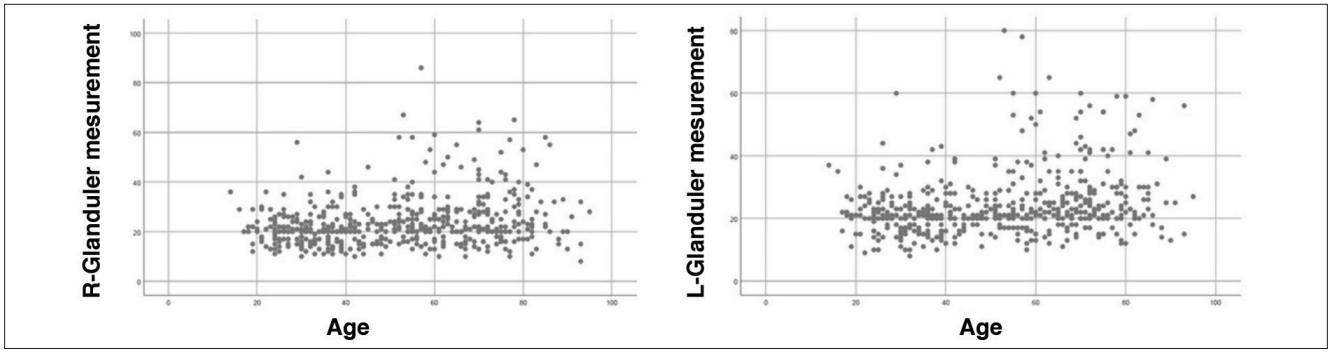


Figure 6. Relationship between age and glandular tissue diameter of right and left breast

decade group, a number of cases were close to each other in all decades. This may be one reason why the prevalence of gynecomastia in this study was different from other reports in the literature.

In our study, accompanying diseases included liver cirrhosis, chronic kidney failure, congestive heart failure, benign prostatic hyperplasia, prostate cancer, lung cancer, and stomach cancer. However, full statistical analysis between these diseases and gynecomastia was not performed because we could not obtain medical records and histories of all cases with and without gynecomastia.

Sonnenblick et al. (13) identified high correlation between CT sectional imaging of gynecomastia and mammography findings. In our study, cases with gynecomastia were not evaluated by mammography. Moreover, gynecomastia cases, especially those with diffuse glandular pattern, were specified in CT reports, and clinical directions were made to determine the underlying cause.

Klang et al. (4, 5) reported that a 2.2 cm breast tissue diameter represents the 90th percentile in the general male population by CT (14). Glandular gynecomastia is defined as the presence of tissue more than 2 cm diameter in the subareolar region in axial CT images. Because a small amount of breast tissue is accepted as a normal finding, we used a 2 cm threshold value, according to definitions in the radiological literature (3-7). As mentioned in the literature, significant growth of glandular tissue was observed in the vertical plane in some gynecomastia cases (25% and 29% on the right and left breasts, respectively). Therefore, although axial diameter measurements are <2 cm, these cases were also considered as gynecomastia, according to their appearance. Conversely, cases with a measurement of 0–2 cm, with characteristics similar to atretic ductal structures, were not considered gynecomastia.

Gynecomastia is mostly asymptomatic, and there is no conclusive evidence to suggest a link between cancer and gynecomastia (6). However, the presence of gynecomastia may mask breast cancer in some cases (8). The prevalence of gynecomastia and breast cancer increases in Klinefelter syndrome (6). The incidence of breast cancer in men is very low; it accounts for just 0.6% of total breast cancers and 1% of male cancers (15). Moreover, 40% of male breast cancers are associated with microscopic gynecomastia (13). In excised specimens from patients who underwent surgical treatment for gynecomastia, the rates of invasive carcinoma and in situ carcinoma were 0.11% and 0.18%, respectively (14). The mismatch between rates of symptomatic breast cancer and cancer prevalence in materials excised from men suggests that the rate of asymptomatic breast cancer in men is higher than reported. If necessary, US and mammography should be done. In our study, suspicious breast lesions were not found in any of the patients who underwent CT. Clinical guidance was recommended for cases with diffuse glandular type, as indicated in CT reports.

Our study has some limitations because it is a retrospective study. Some of our cases were admitted only during the pandemic period, and because they were examined for a preliminary diagnosis of COVID-19 pneumonia, there may be some missing information in the patients' hospital records. In terms of gynecomastia, there was no physical examination, US, or mammography of the patients. Therefore, concomitant diseases and drug information may be missing. To improve determination of gynecomastia causes, new studies should be conducted with all data, including current diseases and drugs taken.

In conclusion, we detected gynecomastia by CT in 32.3% of patients with a prediagnosis of COVID-19 pneumonia. Although gynecomastia is diagnosed primarily with mammography and US, we suggest that chest CT may help diagnose patients with suspected gynecomastia if CT was performed within the last 6 months.

Ethics Committee Approval: This retrospective study was approved by our institutional ethics committee (approval no: 20-8.1T/40) and the Republic of Turkey Ministry of Health, COVID-19 Scientific Research Committee.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: Ö.A., A.O., R.S.; Design: Ö.A., A.O.; Supervision: Ö.A., A.O., R.S., S.B., N.C.; Materials: Ö.A., R.S., S.B., N.C., A.Ç.; Data Collection or Processing: Ö.A.; Analysis or Interpretation: Ö.A., A.O.; Literature Search: Ö.A., A.O., R.S., S.B.; Writing: Ö.A., A.O.; Critical Review: Ö.A., A.O., R.S.

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

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Original Article

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Impact of COVID-19 On Breast Cancer Management: A Radiological Prespective from A Tertiary Centre

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ABSTRACT

Objective: The coronavirus-2019 (COVID-19) pandemic caused delaying breast cancer management, increasing time interval in chemotherapy cycles and surgery. This has implications on radiological manifestation of cancer. Further, we evaluated changes observed in mammography.

Materials and Methods: This case control study was conducted from March 25th, 2020 to August 15th, 2020 at the Integrated Breast Care Centre, All India Institute of Medical Science Rishikesh (AIIMS), Rishikesh. Sonomammography was performed on follow-up patients who were on chemotherapy and were scheduled for surgery. Moreover, duration of delay from the last neoadjuvant chemotherapy (NACT) cycle was recorded. Similar data in the pre-COVID-19 period from November 4th, 2019 to March 24th, 2020 was compared with post-COVID-19 data and was analyzed by SPSS Version 23.

Results: The study included 54 patients who presented between March 25th, 2020 and August 15th, 2020. Furthermore, the delay in NACT cycles has been shown to be associated with disease progression (p = 0.045). Subgroup analysis of treatment duration with various parameters revealed significant correlation between size, appearance of ulceration, and response evaluation (p<0.05). However, no significant association was found between duration of delay and the histological subtype of lesion (p>0.05). A substantial difference was seen in the evaluation of NACT response in pre- and post-COVID-19 time, with partial response (n = 39, 58.24%) seen as the most common response in pre-COVID-19 time and progressive disease (n = 28, 51.9%) as the most common response in post-COVID-19 time (p<0.001).

Conclusion: The coronavirus pandemic has severe impact on breast cancer management. A delay in NACT causes progression in cancer. This can be seen in ultrasound and mammogram.

Keywords: Breast cancer, neoadjuvant chemotherapy, delay, mammography

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Key Points

- Coronavirus pandemic has severe impacts on breast cancer management.
- The delay in neoadjuvant chemotherapy cycles and duration in between the neoadjuvant chemotherapy cycles and surgery is associated with disease progression.
- The impacts of delay in neoadjuvant chemotherapy cycles can have radiological manifestations which can be seen on mammography and ultrasound.

Introduction

In the year 2020, the coronavirus pandemic affected many countries worldwide. One of the hardest hit countries is India. To cope up with such a pandemic, nationwide lockdown was imposed from March 25th, 2020 to May 31st, 2020 for a period of 68 days (1). This restricted the movement of people, which was necessary given the pandemic situation. It was also recommended that cancer surgery be postponed and chemotherapy be continued in cancer patients to reduce the risk of hospital-acquired coronavirus disease-2019 (COVID-19). Moreover, health emergencies and cancer treatment were exempted from the stringent lockdown. However, lack of awareness caused delays in the management of various cancer patients, such as those who were on chemotherapy and radiotherapy and were scheduled for surgery. Furthermore, the effects of delays in treatment due to such a pandemic situation can be seen on imaging in these cancer patients.

Many studies have been carried out worldwide, such as those by Freer (2) and Broom et al. (3), which state that the coronavirus pandemic has adversely affected the cancer management in general and breast cancer in particular. As a precautionary measure to reduce the infection, the level

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of care provided to cancer patients has reduced since the pandemic (4). The management of patients with breast cancer has been impaired, resulting in delayed diagnosis, chemotherapy, and surgery. Timelines from surgery to adjuvant chemotherapy has been increased (5, 6). In addition, breast cancer imaging was affected, showing a marked reduction in case volumes, especially during the first 2 months of the pandemic. All imaging modalities, such as mammography, ultrasonography, and breast magnetic resonance imaging (MRI), were affected; however, breast mammography was most affected (2, 7).

About half a century ago, preoperative chemotherapy was started with the goal of treating locally advanced and non-operable breast cancer (8). However, preoperative NACT is also regarded as the standard of care for primary operable breast cancer these days (9). The objectives of preoperative NACT are not only to minimize cancer and increase breast-conserving surgery but also to achieve pathological complete response (8, 10).

Various imaging modalities are available for assessing the response evaluation of NACT in patients with breast cancer, such as physical examination in conjunction with mammography and ultrasonography, dynamic breast MRI, Positron emission tomography scan, and mammoscintigraphy (11, 12). Out of the various available modalities, physical examination, together with mammography and ultrasonography, is most widely used modality (12).

The latest guideline for response evaluation in solid tumors is response evaluation criteria in solid tumors (RECIST) Version 1.1 (13). In compliance with this guideline, the response evaluation to treatment can be provided in the form of complete response, partial response, progressive disease, and stable disease after comparison with prior imaging.

The main objective of this case control study is to evaluate changes observed in mammography and ultrasonography due to delays in the treatment course of breast cancer. This entails the delay in neoadjuvant chemotherapy cycles and duration gap between the last neoadjuvant chemotherapy and surgery.

Materials and Methods

This case control study was conducted at the Integrated Breast Care Centre, AIIMS, Rishikesh, from March 25th, 2020 to August 15th, 2020 for a period of 4.5 months. This data was correlated with the data collected from November 04th, 2019 to March 24th, 2020 taken in pre-COVID-19 time. Further, the response evaluation was performed according to RECIST Version 1.1. The duration of delay from the last NACT cycle was recorded. There were also histopathological types of each patient obtained. In addition, changes observed in mammogram and ultrasound were recorded. This included changes in size, change in density, and appearance of new calcification, satellite nodules, and lymph node status and muscle/skin infiltration. Mammography was performed using the Hologic Selenia Dimensions, Hologic (USA). On the other hand, ultrasound was performed using 4–12 MHz linear high-frequency probe of Esaote MyLab 9 eXP Diagnostic Ultrasound system, Model MyLab 9 eXP scanner.

Inclusion criteria:

- All follow-up patients who were on NACT and visited again for response evaluation.
- All follow-up patients who have completed their NACT and were scheduled for surgery.

Exclusion criteria:

- All new patients who came for the first time.
- All benign cases.
- All those patients who had received their prior neoadjuvant therapy and presented for future follow-up at our center for the first time were excluded because there was no prior imaging available for comparison.

The analysis of data was conducted using SPSS Version 23. For descriptive statistics, the data was analyzed, and the association between various parameters was correlated using non-parametric tests of correlation, such Spearman's rank-order correlation coefficient, Kruskal-Wallis H test, and Mann-Whitney-Wilcoxon test as the duration of delay was not normally distributed.

Results

Patient characteristics

A total of 54 patients presented for follow-up between March 25th, 2020 and August 15th, 2020. This post-COVID-19 data was contrasted with pre-COVID-19 data collected from November 4th, 2019 to March 24th, 2020. The duration of delay, associated RECIST, histological subtypes of tumor, and radiological findings during both periods are summarized in Table 1. It was found that in the pre-COVID-19 times, the patient was found to have a mean duration delay of 15.69 days (median = 14 days and mode = 10 days) from the last NACT cycle and, if scheduled for surgery, was usually operated within 6 weeks (42 days). However, during the post-COVID-19 times, this duration has increased, and patients used to present a mean duration delay of 85.76 days (median = 89 days and mode = 72 days), increasing the time duration between the NACT cycles and gap between the last NACT cycle and surgery. Due to such a long gap of duration, most patients (n = 28, 51.9%) developed progressive diseases and had to undergo a few more NACT cycles before undergoing surgery. The maximum duration of delay observed during the pre-COVID-19 time was 50 days post 4 cycles of NACT, while the minimum duration of delay was 2 days post 4 cycles of NACT. However, during the post-COVID-19 times, the maximum duration of delay was 117 days observed in patients post 9 cycles of NACT, whereas the minimum duration of delay was 29 days post 10 cycles of NACT. During the post-COVID-19 time, the average duration patients underwent surgery following their last NACT cycle was 73 days if the post-NACT mammogram and ultrasonography suggested a stable disease or partial response.

When considering the post-COVID-19 period, the average age of presentation was 45.35 years, with standard deviation of 10.60 years. Most patients had triple-negative breast cancer (n = 15, 27.8%), with malignant phyllodes (n = 2, 3.7%) being the least common tumor seen. Moreover, progressive disease was mostly seen in triple-negative breast cancer (n = 11, 20). Right- and left-sided breast involvement was seen in 27 cases (50%) each.

In comparison with pre-COVID-19 time, the most common response seen was partial response (n = 39, 58.2%), while the least common was complete response (n = 1, 1.5%). Further, progressive disease was seen in only seven cases (10.4%).

Increasing the duration between the NACT cycles and the last NACT cycle and surgery is strongly correlated with disease progression (Table 1). In the response evaluation, a significant statistical difference was observed in pre- and post-COVID-19 time ($p<0.001$).

Table 1. Summary of all parameters

All parameters	Pre-COVID-19	Post-COVID-19
	Mean ± SD ‖min-max‖ Frequency (%)	Mean ± SD ‖min-max‖ Frequency (%)
Age (years)	44.54±9.01 ‖24–63‖	45.35±10.60 ‖28–66‖
Duration (days)	15.69±8.88 ‖2–50‖	85.76±33.29 ‖29–136‖
Laterality		
Right	39 (58.2%)	27 (50%)
Left	27 (40.3%)	27 (50%)
Bilateral	1 (1.5%)	0
Cycles of NACT		
No NACT	0	3 (5.6%)
2 cycles	0	1 (1.9%)
4 cycles	33 (49.3%)	13 (24.1%)
5 cycles	4 (6.0%)	2 (3.7%)
6 cycles	1 (1.5%)	0
7 cycles	0	3 (5.6%)
8 cycles	27 (40.3%)	27 (50%)
9 cycles	0	1 (1.9%)
10 cycles	0	3 (5.6%)
11 cycles	0	1 (1.9%)
12 cycles	2 (30%)	0
Change in size		
Increased	9 (13.4%)	26 (48.1%)
Decreased	57 (85.1%)	19 (35.2%)
Stable	1 (1.5%)	9 (16.7%)
Change in density		
Increased	1 (1.5%)	15 (27.8%)
Decreased	25 (37.3%)	7 (13%)
Stable	40 (59.7%)	24 (44.4%)
Mammogram not done	1 (1.5%)	8 (14.8%)
Calcification in lesion		
New calcification	0	5 (9.3%)
Same as prior	28 (41.8%)	16 (29.6%)
No calcification	38 (56.7%)	25 (46.3%)
Mammogram not done	1 (1.5%)	8 (14.8%)
Appearance of ulceration		
New ulceration	0	4 (7.4%)
Ulcerated since earlier	1 (1.5%)	3 (5.6%)
No ulceration	66 (98.5%)	47 (87%)
Ipsilateral axillary lymph nodes		
New nodes	0	8 (14.8%)
Same as previous	30 (44.8%)	28 (51.9%)
No nodes	28 (41.8%)	18 (33.3%)
Reduced	9 (13.4%)	0

Table 1. Continued

All parameters	Pre-COVID-19	Post-COVID-19
	Mean ± SD ‖min-max‖ Frequency (%)	Mean ± SD ‖min-max‖ Frequency (%)
Infraclavicular lymph nodes		
New nodes	0	7 (13%)
Same as previous	2 (3%)	4 (7.4%)
No nodes	65 (97%)	43 (79.6%)
Supraclavicular lymph nodes		
New nodes	1 (1.5%)	2 (3.7%)
Same as prior	1 (1.5%)	4 (7.4%)
No nodes	65 (97%)	48 (88.9%)
Contralateral side		
New infiltrated axillary LN	0	2 (3.7%)
No change	66 (98.5%)	47 (87%)
New malignant breast lesion	1 (1.5%)	5 (9.3%)
Histological subtype		
Luminal type A	22 (32.8%)	19 (35.5%)
ER/PR/HER2neu+ve	15 (22.4%)	8 (14.8%)
HER 2neu+ve	13 (19.4%)	10 (18.5%)
TNBC	17 (25.4%)	15 (27.8%)
Phyllodes tumor	0	2 (3.7%)
RECIST		
Stable	20 (29.9%)	19 (35.2%)
Progressive disease	7 (10.4%)	28 (51.9%)
Partial response	39 (58.2%)	6 (11.1%)
Complete response	1 (1.5%)	1 (1.9%)

LN: Lymph nodes; SD: Standard deviation; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; TNBC: Triple-negative breast cancer; COVID-19: Coronavirus disease-2019; min: Minimum; max: Maximum; RECIST: Response evaluation criteria in solid tumors

Impact of duration of delay in treatment on various parameters during post-COVID-19 times

Most patients were able to visit the hospital after a median duration delay of 89 days (mode = 72 days, mean = 85.76 days). We analyzed the impact of duration of delay (days) in treatment on the characteristics of various patients, such as age of presentation, side of breast involvement, status of the NACT cycles, and appearance of ulceration. In addition, we have also studied its impact on radiological features, such as change in size, mammographic density, presence of calcification, and lymph nodal status. A correlation with histological subtype and RECIST was also carried out. The following were our observations:

- A significant correlation ($p<0.05$) was observed in relation to the breast involved, change in size of lesion, appearance of ulceration, infraclavicular lymph nodes, and RECIST (Table 2).

- **Change in size of lesion:** It was found that radiological increase in size of lesion was seen in 48.1% of cases (n = 26, p = 0.042), whereas a decrease was seen in 35.2% of cases (n = 19).

- **Appearance of new ulceration**: Delay in treatment was seen to be associated with the appearance of new ulceration in lesion in 7.4% of cases (n = 4, p = 0.013). As a result of ulceration, mammography could not be performed in these patients.

- **RECIST:** On response evaluation, the majority of patients displayed progressive disease (Figure 1) (n = 28, 51.9%, p = 0.045), whereas the least commonly seen was complete response (n = 1, 1.9%).

- **Other characteristics:** Other radiological changes were also seen, such as the appearance of a new calcification (n = 5, 9.3%, p = 0.223) and increase in mammographic density of lesion (n = 15, 027.8%) (Figure 2); however, this correlation was insignificant (p = 0.802) (Table 2). The appearance of new malignant lesion in contralateral breast (n = 5, 9.3%) (Figure 3) and new lymph nodes in contralateral axilla (n = 2, 3.7%) was found in few cases (p = 0.166).

Discussion and Conclusion

Breast cancer is the most common malignancy in females, with a lifetime risk of up to 1.8 (14). Before surgery, neoadjuvant therapies,

Table 2. Non-parametric correlation analysis between delay in duration (days) and post-COVID-19 parameters

Parameters	Mean ± SD ‖min-max‖ Frequency (%)	Duration of delay	p-value
		Correlation coefficient (rho)	
Age (years)	45.35±10.608 ‖28–66‖	0.191	0.166
Laterality			
Right	27 (50%)	0.298*	0.028
Left	27 (50%)		
Cycles of NACT			
No NACT	3 (5.6%)		
2 cycles	1 (1.9%)		
4 cycles	13 (24.1%)		
5 cycles	2 (3.7%)		
7 cycles	3 (5.6%)		
8 cycles	27 (50%)	0.240	0.090
9 cycles	1 (1.9%)		
10 cycles	3 (5.6%)		
11 cycles	1 (1.9%)		
Change in size			
Increased	26 (48.1%)		
Decreased	19 (35.2%)	0.278*	0.042
Stable	9 (16.7%)		
Change in density			
Increased	15 (27.8%)		
Decreased	7 (13%)		
Stable	24 (44.4%)	–0.035	0.802
Mammogram not done	8 (14.8%)		
Calcification in lesion			
New calcification	5 (9.3%)		
Same as prior	16 (29.6%)		
No calcification	25 (46.3%)	–0.169	0.223
Mammogram not done	8 (14.8%)		
Appearance of ulceration			
New ulceration	4 (7.4%)		
Ulcerated since earlier	3 (5.6%)	–0.335*	0.013
No ulceration	47 (87%)		
Ipsilateral axillary lymph nodes			
New nodes	8 (14.8%)		
Same as previous	28 (51.9%)	0.183	0.186
No nodes	18 (33.3%)		
Infraclavicular lymph nodes	7 (13%)		
New nodes	4 (7.4%)		
Same as previous	43 (79.6%)	–0.275*	0.044
No nodes			

Table 2. Continued

Parameters	Mean ± SD ‖min-max‖ Frequency (%)	Duration of delay	p-value
		Correlation coefficient (rho)	
Supraclavicular lymph nodes			
New nodes	2 (3.7%)		
Same as prior	4 (7.4%)	−0.225	0.101
No nodes	48 (88.9%)		
Contralateral side			
New infiltrated axillary lymph node	2 (3.7%)		
No change	47 (87%)	−0.101	0.166
New malignant breast lesion	5 (9.3%)		
Histological subtype			
Luminal type A	19 (35.5%)		
ER/PR/HER2neu+ve	8 (14.8%)		
HER 2neu+ve	10 (18.5%)		
TNBC	15 (27.8%)	0.219	0.111
Malignant phyllodes tumor	2 (3.7%)		
RECIST			
Stable	19 (35.2%)		
Progressive disease	28 (51.9%)		
Partial response	6 (11.1%)	0.274*	0.045
Complete response	1 (1.9%)		

NACT: Neoadjuvant chemotherapy; COVID-19: Coronavirus disease-2019; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; SD: Standard deviation; min: Minimum; max: Maximum; RECIST: Response evaluation criteria in solid tumors

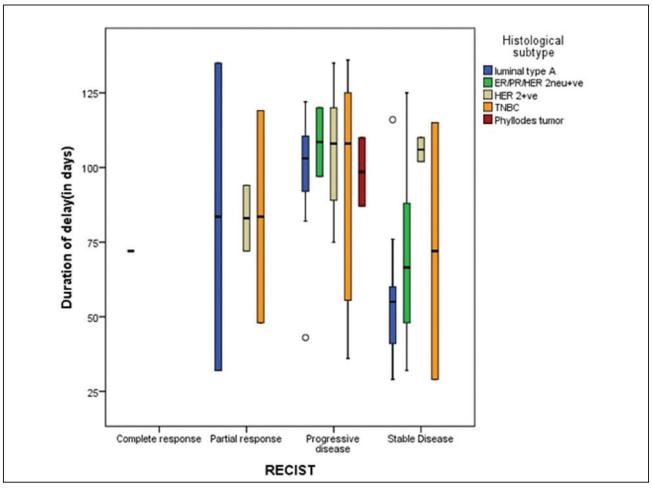

Figure 1. Clustered boxplot showing tumor response in relation to various histological subtypes of malignant breast lesions in post-COVID-19 period. We can see that complete response was seen only in 1 (1.9%) case with luminal type A as histological subtype with delay in duration of 72 days. As the duration of delay increased, most of histological subtypes showed either progressive (n = 28, 51.9%) or stable disease (n = 19, 35.2%)

COVID-19: Coronavirus disease-2019; LN: Lymph nodes; ER: Estrogen receptor; PR: Progesterone receptor; HER2: human epidermal growth factor receptor 2; TNBC: Triple-negative breast cancer; n: Number; RECIST: Response evaluation criteria in solid tumors

such as chemotherapy, radiation, and endocrine therapy, were used to pre-treat tumor (15). Due to this technique, mortality associated with breast cancer has reduced these days. Using neoadjuvant therapies, even all those cancers that are initially inoperable can be downgraded to fulfill operability criteria (8).

In breast cancer management, neoadjuvant therapies are being followed at almost all centers these days. Generally, a 3-month course is offered, and then the tumor is evaluated for reduction in volume (15). In our center, the patient is reevaluated with mammography and ultrasonography after completion of four and sometimes eight cycles of chemotherapy, and response evaluation is conducted. Prior to surgery, another follow-up imaging is performed.

According to the literature, the duration between the last neoadjuvant chemotherapy and surgery should not be more than 28 days. This gap of 28 days is necessary for overcoming the neutropenic window (8, 10). However, there are no clear-cut guidelines for the maximum duration allowed between the last cycle of neoadjuvant therapy and surgery, and different studies show different results (16-20). In our center, patients are generally operated post 2-3 weeks of the last chemotherapy cycle. However, due to the coronavirus pandemic, this time interval has increased. Most of the patients were able to visit the hospital after a median duration delay of 89 days (mode = 72 days, mean = 85.76 days). Thus, a repeat imaging with mammography and

ultrasonography of all the patients who visited post-lockdown was performed to know the status of disease.

There are fewer studies which state that delayed duration of >8 weeks in neoadjuvant therapy and surgery is associated with poor outcomes (21). However, the reason of delay in their study was unknown.

Studies by Jazieh et al. (4) and Li et al. (6) have been carried out post-coronavirus pandemic, which clearly shows the inadvertent effects of delay in treatment of cancer patients. Every aspect of breast cancer management has been affected from screening to diagnosing and treatment (2, 6). Many studies have shown the effects of change of care of cancer patients on imaging modalities in the form of reduction in case volumes of mammography, ultrasonography, and breast MRI (2, 7). However, so far, no study has shown what changes are actually observed on imaging in follow -up patients in the post-pandemic period. Moreover, none of the studies has shown changes in mammography density, appearance of new calcification, ulceration and lymph nodes, and their association with the histological subtype. This novel study aims to review these radiological changes observed on mammogram.

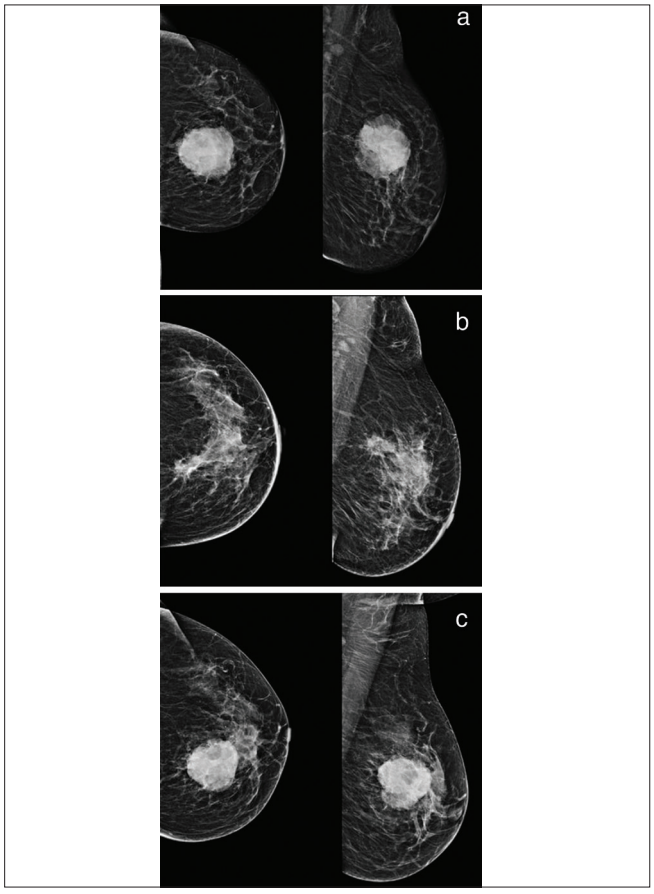

Figure 2. Mammogram images of a 52-year-old female patient who initially presented with lump in her left breast. HPE from the lesion was s/o invasive carcinoma grade III, ER/PR negative, and HER2 neu equivocal. **(a)** CC and MLO images done at baseline was s/o oval-shaped high-density lesion with microlobulated margins in the left breast in the upper inner quadrant. Few foci of microcalcification can also be seen within the lesion on CC view. Few equal-density lymph nodes with loss of hila can also be seen in the left axilla. **(b)** CC and MLO images done post 4 cycles of NACT during the pre-COVID-19 time at a duration delay of 10 days show reduction in lesion size along with mild reduction in density s/o partial response (RECIST 1.1). **(c)** CC and MLO images done after COVID-19 at a duration delay of approximately 115 days (3.8 months) showed s/o increase in size of the left breast lesion along with an increase in its density. The overall response assessment was s/o progressive disease (RECIST 1.1)

HPE: Histopathological Examination; HER2: Human epidermal growth factor receptor 2; CC: Craniocaudal; MLO: Mediolateral oblique; NACT: Neoadjuvant chemotherapy; COVID-19: Coronavirus disease-2019; ER: Estrogen receptor; PR: Progesterone receptor; RECIST: Response evaluation criteria in solid tumors

It can be clearly seen from our study that duration of delay in neoadjuvant therapy and surgery is associated with progression of diseases, worsening the outcome.

The main limitation of our study is short duration of the study. A small sample size could be collected in this short duration of study. Other shortcoming is that it is a single-centered study. A larger study with more samples may show more reliable results. Although patients who presented for the first time post-lockdown were not included in this study, they also presented with advanced disease post-lockdown as they were reluctant to visit hospitals during the lockdown. The reasons of delayed presentation also need to be studied so that they can be remedied in future. This may form a basis for further research.

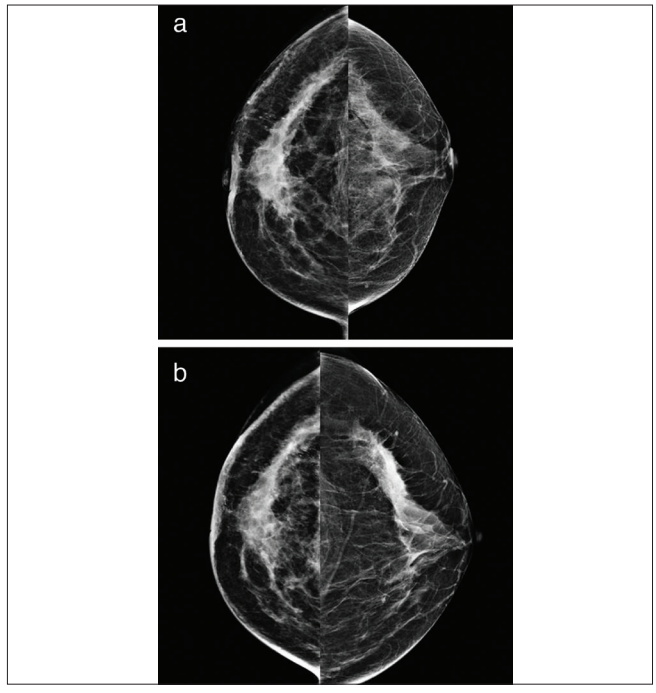

Figure 3. Mammogram images of a 50-year-old female patient who initially presented with lump in her right breast. HPE from the lesion was s/o invasive carcinoma grade III, ER positive, and PR/HER2neu negative. **(a)** CC image of right breast done at baseline was s/o an irregular iso- to high-density lesion showing spiculated margins in upper outer quadrant and retroareolar region, reaching up to the nipple, showing few fine pleomorphic microcalcifications within and in vicinity of the lesion with surrounding architectural distortion. The left breast was normal. **(b)** CC images done post 8 cycles of NACT during the post-COVID-19 time at a duration delay of 52 days show no significant change in the size of the right breast BIRADS 6 lesion; however there is appearance of new irregular-shaped high-density lesion with indistinct margins in the left breast upper outer quadrant. HPE from this lesion was malignant etiology. The overall response assessment was s/o progressive disease (RECIST 1.1)

HPE: Histopathological Examination; HER2: human epidermal growth factor receptor 2; CC: Craniocaudal; MLO: Mediolateral oblique; NACT: Neoadjuvant chemotherapy; COVID-19: Coronavirus disease-2019; ER: Estrogen receptor; PR: Progesterone receptor; BIRADS: Breast Imaging Reporting and Database System score; RECIST: Response evaluation criteria in solid tumors

In conclusion, the coronavirus pandemic has severe impact on breast cancer management. A significant correlation was found in progression of disease with increase in duration of delay as seen during the pre- and post-COVID-19 time. A delay in neoadjuvant chemotherapy cycles and duration between the last cycle of neoadjuvant chemotherapy and surgery cause progression in cancer. This can be observed in mammogram and ultrasound. Delayed duration in surgery is clearly associated with increased size of lesion, increased mammography density, and appearance of ulceration in lesion. The appearance of new calcification, contralateral malignant breast lesion, and axillary and supra/infraclavicular lymph nodes were also seen. Furthermore, COVID-19 pandemic has had a devastating impact on breast cancer patients.

Ethics Committee Approval: Since this study is a retrospective study, ethics committee approval is not necessary.

Informed Consent: Informed consent was taken from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: A.S., B.R., N.C., S.R., P.S.; Design: G.K., A.K.; Supervision: A.K., P.S., S.C.; Materials: G.K., M.C.; Data Collection or Processing: G.K., A.D., S.C., P.G.; Analysis or Interpretation: G.K., A.K., S.C.; Literature Search: G.K., M.C., A.D., P.G.; Writing: G.K., M.C., A.K., B.R., N.C., S.R., P.S.

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

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Original Article

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Breast Cancer Management During the COVID-19 Pandemic: The Senologic International Society Survey

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ABSTRACT

Objective: In early 2020, the spread of coronavirus disease-2019 (COVID-19) led the World Health Organization to declare this disease a pandemic. Initial epidemiological data showed that patients with cancer were at high risk of developing severe forms of COVID-19. National scientific societies published recommendations modifying the patients' breast cancer (BC) management to preserve, in theory, quality oncologic care, avoiding the increased risk of contamination. The Senology International Society (SIS) decided to take an inventory of the actions taken worldwide. This study investigates COVID-19-related changes concerning BC management and analyzes the will to maintain them after the pandemic, evaluating their oncological safety consequences.

Materials and Methods: SIS network members participated in an online survey using a questionnaire (Microsoft® Forms) from June 15th to July 31st, 2020.

Results: Forty-five responses from 24 countries showed that screening programs had been suspended (68%); magnetic resonance imagines were postponed (73%); telemedicine was preferred when possible (71%). Surgeries were postponed: reconstructive (77%), for benign diseases (84%), and in patients with significant comorbidities (66%). Chemotherapy and radiotherapy protocols had been adapted in 28% of patients in both. Exception for telemedicine (34%), these changes in practice should not be continued.

Conclusion: The SIS survey showed significant changes in BC's diagnosis and treatment during the first wave of the COVID-19 pandemic, but most of these changes should not be maintained. Indeed, women have fewer severe forms of COVID-19 and are less likely to die than men. The risk of dying from COVID-19 is more related to the presence of comorbidities and age than to BC. Stopping screening and delaying treatment leads to more advanced stages of BC. Only women aged over 65 with BC under treatment and comorbidities require adaptation of their cancer management.

Keywords: Breast cancer, COVID-19, SARS-CoV-2, clinical practices, survey, pandemic

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Key Points

- Breast cancer diagnosis and treatment were deeply impacted since the beginning of the SARS-CoV-2 pandemic.
- In the light of recent findings on COVID-19 risk among women with breast cancer, most of these changes should not be maintained as the risk of severe COVID-19 is related to comorbidities and age rather than breast cancer.
- Only women with breast cancer aged over 65 or with comorbidities require adaptation of their cancer management, according to the Senologic International Society.

Introduction

At the end of 2019, a new coronavirus (SARS-CoV-2) caused pneumonia in several patients epidemiologically linked to a Wuhan market (Hubei province, China). In early 2020, the spread of coronavirus disease-2019 (COVID-19) led the World Health Organization to declare this disease a pandemic. Despite extraordinary measures implemented in many countries, the epidemic spread, with mortality significantly higher than influenza. Initial epidemiological data showed that patients who were older and/or had comorbidities, and notably cancer, were at higher risk of developing severe forms of COVID-19 (1, 2). As breast cancer (BC) is the leading cancer among women worldwide, with more than 2 million new cases and more than 650,000 deaths each year (3), the situation was of particular concern for women with BC. Emergency health actions have been implemented in various countries, involving changes in the treatment and care circuits for numerous cancers, including BC. Many national scientific societies published a series of recommendations modifying BC patient management to preserve, in theory, quality oncologic care while avoiding an increased risk of contamination by SARS-CoV-2 (4-6). In addition, postponing BC surgeries freed equipment and health care staff to support COVID-19 patient care.

The Senologic International Society (SIS) has always been dedicated to promoting breast health and improving BC patients' care, considering medical, social, economic, and ethical constraints. In this pandemic context, the SIS, by its active members, experts, and its global network, decided to assess the actions taken worldwide, the clinical practice changes, and the particularities observed in different countries regarding BC management. The SIS survey's first objective was to investigate and share COVID-19-related changes in clinical practices concerning BC management since the beginning of the pandemic. The second objective was to analyze the will to maintain these changes later in treatment modalities and care pathways, considering the consequences of these oncological safety changes.

Materials and Methods

SIS network members were invited to participate in an online survey using the Microsoft® Forms questionnaire. Between June 15th and July 31st, 2020, participants were invited to answer the questionnaire via e-mail. The answers were directly recorded into an online database, and only one response per participant was allowed. However, more than one response was authorized for each country in case of national disparities.

The online survey consisted of 17 questions. Question 1 was about the participant's origin. The number of deaths due to Coronavirus recorded in his/her country at the moment of the survey, and question 17 was about the participant's profile. Next, we questioned the participants about BC screening programs, radiological practices (question 4), pathological analyses (question 5), telemedicine (question 6), secondary reconstruction surgeries (question 7), benign lesion surgeries (question 8), surgery for patients with

comorbidities (question 9), chemotherapy practices (questions 10 and 11), radiotherapy practices (question 12 and 13), and clinical trials (question 14). We then asked about the management after the lockdown period, if applicable (question 15), and the practice changes that should be maintained thereafter (question 16). The questionnaire is available as Supplementary Material S1 in Appendix 1.

Results

We received 45 completed questionnaires in total. Participants came from 24 countries on six continents (Figure 1): Algeria, Australia, Brazil, Democratic Republic of Congo, Croatia, Ecuador, Egypt, France, Germany, Ghana, Greece, Israel, Jamaican Republic, Japan, Lithuania, Nigeria, Poland, Romania, Russia, Senegal, Spain, Switzerland, Turkey, and the United States. The survey results are reported in Table 1.

In our survey, 38% of participants were oncological surgeons, 4% medical oncologists, 4% radiotherapists, 4% radiologists, 2% nuclear physicians, and 2% anesthesiologists. The other 46% had more than one specialty (a radiologist and nuclear physician or radiotherapist and medical oncologist). Fifty-six percent of respondents had a public or governmental practice, 13% a practice in the private sector, and 31% were involved with both activities. No difference was noted between the public and private sectors regarding BC management.

Diagnosis and consultations

Most participants (69%) reported that organized or individual screening programs were suspended during the pandemic. Sixteen percent of participants reported that screening programs were maintained (Japan, Senegal, Switzerland-in one canton, Jamaican Republic, Croatia, and Algeria). No response was available in the other cases, as these countries have no screening programs.

Participants answered that breast magnetic resonance imaging (MRI) was more often maintained (73%). In contrast, it was suspended for 22% of participants (Switzerland in three cantons, France, Democratic Republic of Congo, Nigeria, Ecuador, and Turkey) due to the difficulty of adequately disinfecting the devices. No response was available in the other cases.

Concerning teleconsultations and phone consultations, most participants (71%) preferred this solution, when possible, during the pandemic. On the other hand, 24% of participants preferred classical consultations. No response was available in the other cases.

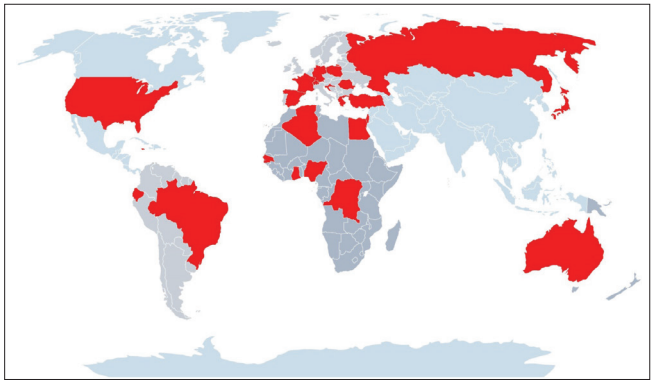

Figure 1. World map with countries that participated in this survey

Table 1. Survey results

Question/Answers	n	(%)
Are/were organized or individual screening programs suspended in your country/state/province during the pandemic?		
Yes	31	(69)
No	7	(16)
Not applicable/no opinion	7	(16)
Are/were breast MRIs performed during the pandemic?		
Yes	33	(73)
No	10	(22)
Not applicable/no opinion	2	(4)
Are/were extemporaneous examinations avoided during the pandemic?		
Yes	30	(67)
No	14	(31)
Not applicable/no opinion	1	(2)
Whenever possible, are/were teleconsultations or telephone consultations preferred during the pandemic?		
Yes	32	(71)
No	11	(24)
Not applicable/no opinion	2	(4)
Are/were secondary reconstruction surgeries postponed during the pandemic?		
Yes	35	(78)
No	5	(11)
Not applicable/no opinion	5	(11)
Are/were surgeries involving benign lesions postponed during the pandemic?		
Yes	38	(84)
No	5	(11)
Not applicable/no opinion	2	(4)
For patients with significant comorbidities making the risk of complications high in case of COVID-19 (elderly subjects, chronic respiratory or cardiac pathology, immunosuppression) is/was the surgical procedure postponed?		
Yes	30	(67)
No	9	(20)
Not applicable/no opinion	6	(13)
Are/were chemotherapy protocols modified to reduce the hospital stay?		
Yes	13	(29)
No	22	(49)
Not applicable/no opinion	10	(22)

Table 1. Continued

Question/Answers	n	(%)
If yes, how?*		
Outpatient treatments	4	(9)
Postponed	4	(9)
Protocol modification	8	(17)
Treatment order modification	1	(2)
No/no opinion	31	(69)
Are/were radiotherapy protocols modified to reduce the hospital stay?		
Yes	13	(29)
No	20	(44)
Not applicable/no opinion	12	(27)
If yes, how?*		
Outpatient treatments	1	(2)
Postponed	2	(4)
Protocol modification	8	(18)
Treatment order modification	2	(4)
No/no opinion	32	(71)
Are/were patients with both breast cancer and COVID-19 infection excluded from the COVID-19 trials?		
Yes	4	(9)
No	10	(22)
Not applicable/no opinion	31	(69)
After the period of deconfinement, will you (or have you) anticipate(d) and prioritize(d) the management of patients with breast pathologies not treated during the pandemic?		
Yes	31	(69)
No	3	(7)
Not applicable/no opinion	11	(24)
Are/were some practice changes beneficial and should they be maintained thereafter? Which changes?*		
Telemedicine implementation	16	(36)
Outpatient treatments	1	(2)
Neoadjuvant endocrine therapy	2	(4)
Public-Private health system collaboration	1	(2)
Improved symptomatic treatment	2	(4)
SARS-CoV-2 screening before treatment	1	(2)
Improved hygiene measures / Personal Protective Equipment	3	(7)
Improved personalized treatments	2	(4)
Less extemporaneous examinations	1	(2)
No/no opinion	17	(38)

*For these open questions, some answers were multiple and therefore the total of responses can be superior to the total of participants

MRI: Magnetic resonance imaging; COVID-19: Coronavirus disease-2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; n: Number

Treatment

Surgery was dramatically modified on different levels since the start of the pandemic. Participants reported that surgeries involving benign lesions were postponed in the majority of cases (84%). Similarly, secondary reconstruction surgeries were also postponed by most participants (78%). For 11% of participants, the question was not applicable since breast reconstruction was not performed in these centers. Most participants (67%) reported that extemporaneous examinations were avoided for BC surgery, whereas 31% continued with them. For one participant (2%), this question was not applicable. For fragile patients (patients with significant comorbidities at high risk of complications in the case of COVID-19), 67% of participants reported that surgeries were postponed, compared with 20% in whom they were not. This question was not applicable, or the participants had no opinion in the remaining other cases.

Other BC treatments were also impacted. Concerning chemotherapy, 29% of participants reported that protocols were modified to reduce hospital stays, whereas 49% remained unchanged. For the remaining participants, this question was not applicable, or the participant had no opinion. Participants who answered positively (n = 13) reported different methods (multiple responses were possible for each participant): protocol modifications (62%), outpatient treatments (31%), treatment postponement (31%) and/or treatment order modification (i.e., chemotherapy before radiotherapy, 8%)

Concerning radiotherapy, 29% of participants reported that protocols were modified to reduce hospital stays (hypofractionated protocols), whereas, in 44%, they were unchanged. For 27% of participants, this question was not applicable, or the participant had no opinion. Similarly, participants who answered positively (n = 13) reported different methods (multiple responses were possible for each participant): protocol modifications (62%), outpatient treatments (8%), treatment postponement (15%) and/or treatment order modification (15%).

Clinical trials

Four participants (9%) mentioned that patients with BC and COVID-19 were excluded from clinical trials concerning COVID-19. Ten participants responded negatively (22%). This question was not applicable, or the participant had no opinion in 69% of cases.

After the lockdown period

Most participants (69%) anticipated and prioritized the management of patients with breast pathologies not treated during the pandemic. We observed that 24% of participants did not respond, as, in some countries, there was no lockdown at the time of the survey.

Thirty-six percent of participants found that telemedicine implementation should be maintained after the pandemic, for example, for BC survivors. The remaining practice changes should not be maintained to avoid the pejorative evolution of some patients.

Mortality

Our survey did not provide any results regarding mortality among BC patients, as it concerned practice changes and was not an observational study.

Discussion and Conclusion

The SIS conducted an international survey to investigate and share COVID-19 related changes in clinical practices concerning BC management during the pandemic.

Strengths and limitations of the survey

Participants were from 24 countries, as shown in Figure 1. These countries represented 1.701 billion people and 22% of the world's population. Participants had different disciplines and covered most breast specialties: surgery (general and gynecological), medical oncology, radiotherapy, radiology, nuclear medicine, and anesthesiology. In addition, they were from different types of practices, working in both university hospitals and private practices. In some cases, practices were heterogeneous among healthcare providers within each country, especially if the pandemic affected their regions differently. However, the SIS survey showed that many countries had adopted similar measures. Concerning diagnosis, screening programs had often been suspended, and MRI use was reduced. Therapeutically, non-urgent surgery had been postponed, whereas medical and radiotherapy treatments had been adopted.

All these changes were based on initial epidemiological data hypothesizing that patients with cancer were at a higher risk of developing severe forms of COVID-19. For example, at the beginning of the pandemic, a study published by Liang et al. (1) showed that patients with cancer had a higher risk of developing a severe form of COVID-19, including invasive ventilation, intensive care unit admissions, or death [odds ratio (OR): 5.34, 95% confidence interval (CI): 1.80-16.18; p = 0.0026]. However, even when the study included 1,590 patients, only 18 (1%) had a history of cancer, and among them, BC was present in only three patients. Similarly, Fu et al. (7) showed that cancer patients, in general, were at a higher risk of being infected with SARS-CoV-2 and had higher mortality rates. Likewise, de Azambuja et al. (8) showed that in a cohort of 13,594 patients (of whom 1,187 had solid cancers), cancer was associated with higher COVID-19 related mortality. However, in April 2020, Miyashita et al. (2) published a report on 5,688 patients, including 344 with cancer, of whom 57 had BC. They found that patients with cancer were at significantly higher risk of requiring invasive ventilation (relative risk: 1.89; 95% CI: 1.37–2.61) but not of death (relative risk: 1.15; 95% CI: 0.84–1.57) except for patients aged up to 50 years old (relative risk: 5.01; 95% CI: 1.55–16.2). Unfortunately, no subgroup analysis based on the cancer type was provided.

Since patients with cancer might be at a higher risk in COVID-19, several scientific societies published guidelines to adapt BC management during the pandemic. Worldwide, BC care pathways were disrupted (9, 10): screening was discontinued, surgeries were delayed, chemotherapy and radiotherapy protocols were adapted to reduce hospital stays or the number of sessions. BC treatments were modified since the beginning of the pandemic. First, chemotherapy protocols were changed to reduce hospital stays. For instance, taxane-based protocols with weekly administrations (i.e., paclitaxel) were replaced by docetaxel administrations every three weeks. Otherwise, some other protocols were discontinued or postponed. In some metastatic situations, chemotherapy regimens were changed to an oral treatment such as capecitabine. The main goal was to decrease potential exposure to SARS-CoV-2 and complications in concomitant chemotherapy and COVID-19. Similarly, an American team published results concerning medical treatment modifications in New York and found that adjuvant and neoadjuvant chemotherapy were modified in 41% of cases to reduce the risk of SARS-CoV-2 infection (11). In contrast, oral treatments were modified in only 15% of cases (11).

Radiotherapy was also changed during the pandemic. Hypofractionated regimens were preferred for BC treatment, whereas in other cases, treatment was discontinued. Spencer et al. (12) published a report on radiotherapy modifications in the United Kingdom during the pandemic and found similar results. For instance, treatment with ultra-hypofractionated regimens (26 Gy in 5 fractions) greatly increased from 0.2% in April 2019 to 60.6% in April 2020.

Finally, surgery was also impacted. As reported in the survey, benign and reconstructive surgeries were postponed. In fragile patients, cancer surgeries have also been postponed, and in some cases, neoadjuvant endocrine therapy was introduced. As reported in a survey in the United States published by Park et al. (13), most oncologists (medical, radiotherapists, and surgeons) changed their BC management, and neoadjuvant endocrine therapies went from rarely to frequently prescribed during the pandemic. In addition, most participants found it reasonable to delay surgery without the use of endocrine therapy for 1-2 months, but not for three months (13).

Moreover, during the pandemic, face masks were of paramount importance for COVID-19 prevention, and they were mandatory in healthcare structures in many countries. Clearly, since the beginning of the pandemic, the daily wearing of face masks had been another important change in worldwide practices.

So, important measures were taken at the beginning of the pandemic, even if they were based on preliminary data. Retrospectively, and based on the impact of cancer on the evolution of COVID-19, some proceedings were abandoned. The SIS survey showed that, apart from the development of telemedicine and the wearing of face masks, all these changes would not be definitively implemented by breast specialists' members of the SIS for the following reasons.

Particularities of COVID-19 in women currently treated for BC

First, women have a lower risk of having COVID-19 than men. Growing evidence in the scientific literature shows that men are at higher risk of severe forms of COVID-19 and have higher mortality (14-16). These findings are true for most countries, except for Canada, Vietnam, and Belgium (17), where these differences can be explained by epidemiological factors such as age (15, 16), health behavior (15), socioeconomic context (15), different comorbidities (16), and different immune responses (18). Consequently, data concerning women with cancer was probably too alarming.

Second, women with BC have a lower risk of having COVID-19 than women with other cancers. It was supposed that SARS-CoV-2 infection could have higher direct mortality in BC patients, as they may develop more severe forms of the disease. However, new evidence was published that softened the initial fear. Indeed, COVID-19's impact on mortality is not the same according to cancer type. By analyzing the cancer type, Lee et al. (19) found in a British cohort of 800 patients that BC was at low risk of mortality compared with other cancers (OR: 0.48 (0.28–0.84), p = 0.009). In addition, the authors found that COVID-19-related mortality was principally caused by age, gender, and comorbidities. Vuagnat et al. (20) published a study on 76 patients with early or metastatic BC and suspected COVID-19 among a French cohort of 15,600 patients. They found that 10% were transferred to an intensive care unit, and

7% died (all of whom had significant non-cancer comorbidities). The statistical analysis found that hypertension and age (>70) were the two factors associated with a higher risk of intensive care unit admission and/or death. Interestingly, a history of radiotherapy or current oncological treatment was not associated with mortality. Kalinsky et al. (21) published a report on 27 patients with BC in a cohort of 4,515 patients with COVID-19 from New York City. They found a mortality rate of 4% (n = 1), an 87-year-old male with coronary artery disease, hypertension, and smoking history. De Melo et al. (22) analyzed a population of 40 patients with BC in a Brazilian cohort of 181 patients with cancer and COVID-19. They found that mortality was associated with symptomatic COVID-19 and the presence of two or more metastatic sites in the multivariate analysis. According to the literature, COVID-19's mortality in BC patients seems to be lower than initially estimated compared with other cancers.

Third, late diagnosis because of the lockdown and screening discontinuation may lead to increased BC-related mortality. Vanni et al. (23) conducted a multicentric cohort study in Italy to evaluate the impact of screening suspension and surgical delay on BC staging. They included 432 patients and found that the disease was more advanced at diagnosis with more lymph node involvement. In addition, Maringe et al. (24) studied the impact of COVID-19 and the lockdown period in England and established a predictive model of BC mortality. They estimated that there would be a 7.9%-9.6% increase in the number of deaths due to BC up to year five after diagnosis in England. Johnson et al. (25) conducted a meta-analysis to evaluate how surgical delay affected survival in breast, lung, and colon cancers. They included 25 articles, of which 12 concerned BC. They found that delaying surgery for 12 weeks might decrease overall BC survival (hazard ratio: 1.46, 95% CI: 1.28–1.65). When BCs were analyzed by stage, the authors found that survival was decreased in early stages (I and II, respectively 1.27, 95% CI: 1.16–1.40; and II 1.13, 95% CI: 1.02–1.24) but not in advanced BC.

Considering these findings, many BC specialists suggest that young and middle-aged patients with BC and without comorbidities should be treated without delay during the pandemic. Only patients aged 65 years old or older and with one or more comorbidities (hypertension, diabetes, chronic respiratory disease, and obesity) should have their treatment adapted to lower COVID-19 risk.

Should caution be maintained for patients formerly treated for BC?

Women treated over five years ago for BC are not at increased risk of having the severe form of COVID-19. However, the effects of COVID-19 on BC recurrence were hypothesized. For example, Francescangeli et al. (26) suggested that potential mechanisms could be implicated in reawakening dormant BC cells. In particular, pulmonary dormant BC cells could be reactivated by COVID-19 infection via immune pathways. In a review published by Silvin et al. (27), the authors highlight that severe COVID-19 is linked to an inflammatory burst and lymphopenia related to carcinogenesis and may aggravate cancer prognosis. Even if data are published on COVID-19 immune-mediated cancer recurrence, further studies are needed to assess this potential risk. When possible, telemedicine should be encouraged for BC survivors' follow-up to avoid contact with SARS-CoV-2.

In conclusion, the SIS survey showed significant changes in BC diagnosis and treatment changes during the first wave of the COVID-19 pandemic. Participants in this survey emphasized that most of these changes should not be maintained. Indeed, women have less severe forms of COVID-19 and are less likely to die from COVID-19 than men. The risk of dying from COVID-19 is more related to the presence of comorbidities and age than to BC. Suspending screening and delaying cancer treatment led to more advanced stages of BC. All these delays in BC management may potentially influence BC mortality, even if this effect will not become apparent before probably 7–10 years. Only women aged over 65 with cancer under treatment and comorbidities require an adaptation of their cancer management. When possible, telemedicine should be encouraged for BC survivors' follow-up.

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Ethics Committee Approval: Please find attached the positive advice, reference CE-2021-38, of our Ethics Committee «Comité d'Ethique des Facultés de Médecine, d'Odontologie, de Pharmacie, des Ecoles d'Infirmières, de Kinésithérapie, de Maïeutique et des Hôpitaux» of March 22nd, 2021.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: C.M., S.A., M.L., M.M.C.; Design: C.M., M.L., M.M.C.; Data Collection or Processing: C.M., St.A., E.A., W.M.B., K.B., H.A.A., J.C.C., V.D., E.E., C.E., T.E., E.I., S.I., L.I.M., E.A.K., M.K., Mi.K., F.L., M.M., Ma.M., A.M., R.O., V.O., S.Ö., V.Ö., O.P., T.P., S.S., E.S., Z.P., M.L., M.M.C.; Analysis or Interpretation: C.M., St.A., E.A., W.M.B., K.B., H.A.A., J.C.C., V.D., E.E., C.E., T.E., E.I., S.I., L.I.M., E.A.K., M.K., Mi.K., F.L., M.M., Ma.M., A.M., R.O., V.O., S.Ö., V.Ö., O.P., T.P., S.S., E.S., Z.P., M.L., M.M.C.; Literature Search: C.M., S.A., M.L., M.M.C.; Writing: C.M., S.A., M.L., M.M.C.

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Appendix 1. Supplementary material

Breast cancer and COVID-2019

Breast cancer is a major public health problem in the world and leading cause of cancer deaths in women. The spread of COVID-19 led many scientific societies to publish a series of recommendations modifying the management of breast cancer patients during the COVID-19 pandemic. The 2 objectives of these recommendations were to ensure quality oncology care for breast cancer patients while avoiding increasing their risk of contamination by COVID-19.

The international Society of Senology (SIS) is dedicated to promoting breast health and improving the care of breast cancer patients, taking into consideration, medical, social, economic and ethical constraints. In the context of the COVID-19 pandemic, the SIS, by its active members, experts and global Network must share the actions taken worldwide and the changes in practices observed in different countries and the particularities of breast cancer management during the period of deconfinement.

Deadline for response : 30th of June 2020

***Obligatoire**

1. From which country / state or province are you from?*

2. Do you know how many deaths due to SARS-CoV-2 are recorded in your country / state /province ? (numerical response)

La valeur doit être un nombre

3. Are/Were organized or individual screening programs suspended in your country / state / province during the pandemic?*

◯ Yes
◯ No
◯ No individual or organized screening program exists in my country

4. Are/Were breast MRIs performed during the pandemic?*

◯ Yes
◯ No
◯ No opinion

5. Are/Were extemporaneous examinations avoided during the pandemic?*

◯ Yes
◯ No
◯ No opinion

6. Whenever possible, are/were teleconsultations or telephone consultations preferred during the pandemic?*

◯ Yes
◯ No
◯ No opinion

7. Are/Were secondary reconstruction surgeries postponed during the pandemic?*

◯ Yes
◯ No
◯ No opinion

8. Are/Were surgeries involving benign lesions postponed during the pandemic?*

◯ Yes
◯ No
◯ No opinion

9. For patients with significant co-morbidities making the risk of complications high in case of COVID-19 (elderly subjects, chronic respiratory or cardiac pathology, immunosuppression...) is/was the surgical procedure postponed?*

◯ Yes
◯ No
◯ No opinion

10. Are/Were chemotherapy protocols modified to reduce the hospital stay?*

◯ Yes
◯ No
◯ No opinion

11. If yes, how?

12. Are/Were radiotherapy protocols modified to reduce the hospital stay?*

◯ Yes
◯ No
◯ No opinion

13. If yes, how?

14. Are/Were patients with both breast cancer and COVID-19 infection excluded from the COVID-19 trials?*

◯ Yes
◯ No
◯ No opinion

15. After the period of deconfinement, will you (or have you) anticipate(d) and prioritize(d) the management of patients with breast pathologies not treated during the pandemic?*

◯ Yes
◯ No
◯ No opinion or not applicable

16. Are/Were some practice changes beneficial and should they be maintained thereafter? Which changes?*

17. If you wish to participate to the publication of this survey in the European Journal of Breast Health, please state below your First name, Last name, email, affiliations (and ORCiD number if you have one)

Case Report

Eur J Breast Health 2021; 17(2): 197-199
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Desmoid Type Fibromatosis of the Breast Masquerading as Breast Carcinoma: Value of Dynamic Magnetic Resonance Imaging and Its Correlation

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ABSTRACT

Desmoid type fibromatosis of the breast is a rare stromal tumor that accounts for <0.2% of all breast tumors. Bilateral and multicentric lesions are extremely rare, with only less than ten cases reported in the literature. Although benign, it is locally aggressive with frequent recurrence in up to almost one-third of the cases. We experienced our first case of bilateral multicentric breast fibromatosis in a 19-year-old woman, with a paternal aunt diagnosed with breast cancer at age 30, who presented to our institution with the chief complaint of retracted nipples for 1 year. The patient denied any history of trauma to her chest. Sonography showed suspicious bilateral hypoechoic masses. Magnetic resonance imaging (MRI) was performed for further evaluation because of the extensive involvement of both the breasts. This report aimed to illustrate the main clinical, radiological, and histopathological characteristics of this rare disease to increase awareness of this entity and discuss the role of MRI.

Keywords: Desmoid type fibromatosis, breast tumor, fibromatosis, magnetic resonance imaging, ultrasound

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Key Points

- Desmoid type fibromatosis of the breast is a rare stromal tumour, however it is locally infiltrative with recurrence noted in up to almost one-third of the cases.
- MRI shows varying enhancement pattern and type 2 kinetic curve which mimics malignancy. An accurate evaluation of pectoralis major muscle involvement on MRI is important for surgical planning.
- The standard treatment of desmoid type fibromatosis is wide surgical resection with clear margins.

Introduction

Desmoid type fibromatosis of the breast is a rare stromal tumor that accounts for <0.2% of all breast tumors. Although benign, this tumor is locally aggressive with frequent recurrence in up to almost one-third of the cases (1). Bilateral and multicentric lesions are extremely rare, found in only 4% of patients, with only less than ten cases reported in the literature (1, 2). Imaging features of aggressive fibromatosis can frequently mimic invasive breast cancer, resulting in exhaustive clinical and surgical workups.

Case Presentation

A 19-year-old woman, with a familial history of breast cancer (paternal aunt diagnosed with it at age 30), presented with bilateral breast lumps that were increasing in size and associated with nipple retraction for one year. Physical examination revealed bilateral retracted nipples. There was a 4 cm × 5 cm firm, ill-defined, mobile retroareolar mass in her right breast and a 3 cm × 3 cm firm, ill-defined, mobile mass in the upper outer quadrant of her left breast. There were no skin changes and fixation to the chest wall or skin. Axillary, supraclavicular, and infraclavicular lymph nodes were not palpable. Breast ultrasound showed bilateral ill-defined hypoechoic masses (two on the right, one on the left) with irregular margins and posterior shadowing (Figure 1).

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Initial core biopsy showed benign breast tissue. Because of imaging-histology discordance, magnetic resonance imaging (MRI) was performed for further evaluation. Contrast-enhanced MRI of both the breasts was performed using an MRI 3.0 T machine (Signa® HDx GE Healthcare, Wisconsin, USA). It demonstrated multiple irregular spiculated heterogeneously enhancing masses in the right breast extending from the nipple to the lower outer quadrant and upper half of the breast and collectively measuring 2.3 cm × 5.1 cm × 4.8 cm (Figure 2a, b). These lesions show corresponding hyperintense signals on T2/short tau inversion recovery imaging and hypointense signals on T1 imaging. The nipple-areolar complex was involved. There was no chest wall infiltration. Similar irregular spiculated enhancing mass was seen in the upper half of the left breast, which measured approximately 2.0 cm × 3.3 cm × 4.1 cm (Figure 2c, d). Similarly, it extended into the nipple-areolar complex. Both the breast lesions demonstrated progressive enhancement that plateau on delayed phases consistent with a type 2 curve.

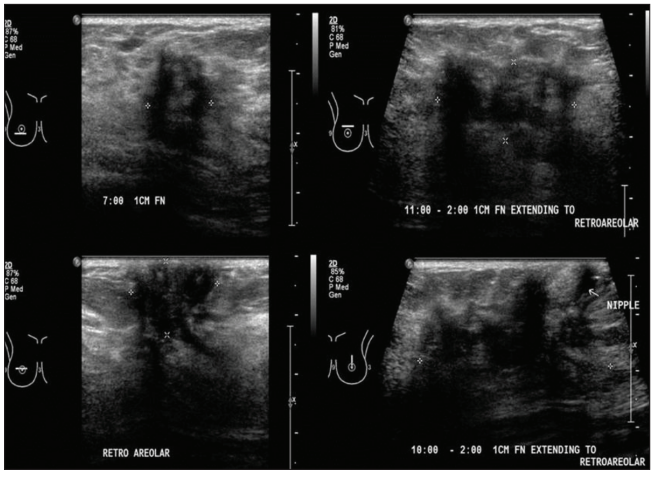

Figure 1. Irregular hypoechoic masses with posterior shadowing in the right seven o'clock position, right upper region, and retroareolar and left upper region. These suspicious bilateral heterogeneous breast lesions were categorized as BIRADS 4c

BIRADS: Breast Imaging Reporting and Database System score

Ultrasound-guided hookwire excision biopsy was performed for three lesions (right at 12:00, left at 12:00, and left at 6:00), and result showed desmoid type fibromatosis.

A multidisciplinary team meeting convened owing to the rarity of this disease entity. The patient agreed for immediate skin-sparing mastectomy and reconstruction because of the local aggressiveness and frequent recurrence of this disease despite having no metastatic potential. The patient refused autologous or implant reconstruction and opted for staged lipofilling. The final histopathology showed proliferation of stellate to spindle-shaped cells. Nuclear positivity for β-catenin and Ki-67 was <1% (Figure 3).

Discussion and Conclusion

Desmoid type fibromatosis are rare, benign, and slow-growing fibroblastic neoplasm, common in women aged 22–49 years (1). It is locally aggressive with frequent recurrence and without distant metastasis. Associations with Gardner's syndrome, familial adenomatous polyposis, surgical trauma, or silicone breast implants have been reported. When associated with silicone implant, fibromatosis is thought to originate from the fibrous capsule of the implant (1, 2).

Clinically, fibromatosis of the breast is often mobile, non-tender firm masses, which sometimes appears to be adherent to the chest wall. Skin dimpling and nipple retraction have been observed, and these findings were similar to those in our patient (3).

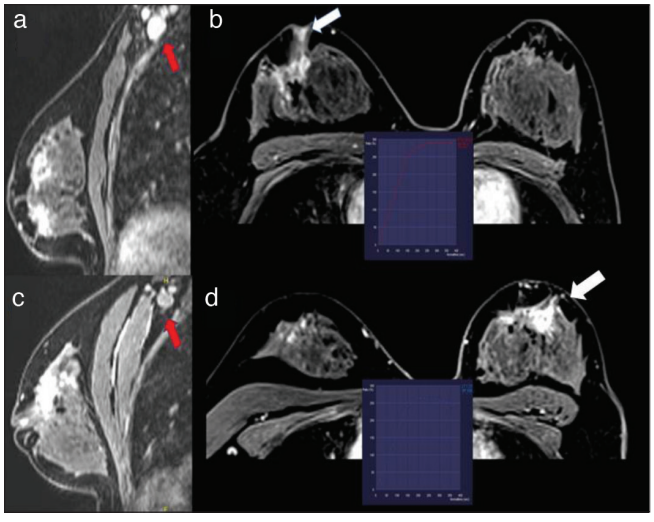

Figure 2. Dynamic post-contrast phase 3 magnetic resonance images, in sagittal and axial views, of the right **(a, b)** and left **(c, d)** breasts demonstrate heterogeneously enhancing spiculated lesions in both the breasts. These lesions demonstrated type 2 kinetic curve pattern (inset). Multicentric lesions were seen on MRI with nipple-areolar complex involvement (white arrow). Abnormal lymph nodes are also seen in both axillae (red arrow)

MRI: Magnetic resonance imaging

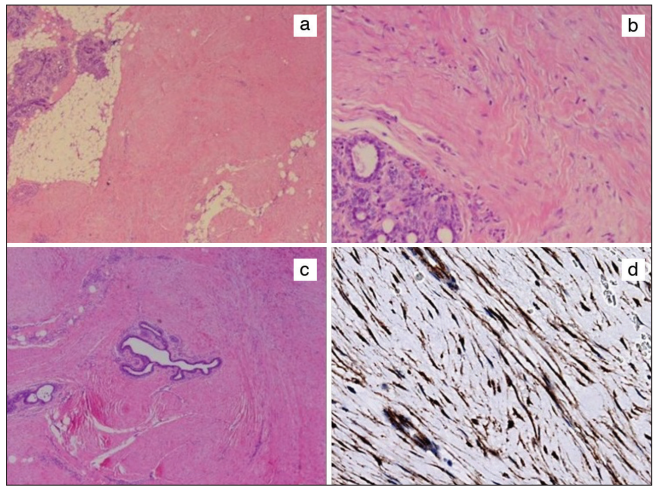

Figure 3. (a) Section of the breast showing the replacement of the breast tissue by fibrous tissue. Proliferation of stellate to spindle-shaped cells in short intersecting fascicle. [hematoxylin & eosin (H&E) staining, under 40x magnification]. **(b)** The cells have elongated, spindle shapes and plump vesicular nuclei with occasional small nucleoli, pale acidophilic cytoplasm, and no distinct cell border (H&E staining, under 40x magnification). **(c)** Entrapped benign breast ducts and acini, mild lymphocytic infiltration, and erythrocytes are seen surrounded by fibrous tissue (H&E staining, under 100x magnification). **(d)** Immunohistochemistry: nuclear positivity for β-catenin; H&E staining, under 400x magnification

The reported cases of fibromatosis have been visible mammographically in only one-third of the cases. They are often irregularly shaped, non-calcified, high-density masses with spiculated margins that mimic breast cancer (1). However, mammography was not performed in our patient given her young age and expected dense breasts. Sonographically, the fibromatoses were solid, spiculated or microlobulated, hypoechoic masses with a thick echogenic rim and posterior attenuation. However, it can also present with benign features. Tethering of the Cooper's ligaments and involvement of the pectoralis muscle have been observed, indicating the locally aggressive nature of fibromatosis and accounting for the skin dimpling and nipple retraction (1, 2).

Although there is an extensive literature on MRI of musculoskeletal desmoid tumors, breast imaging features on MRI have been scarcely reported. Desmoid type fibromatosis appear as ill-defined, hypo to isointense masses on T1-weighted images and as heterogeneously hyperintense masses on T2-weighted images. These findings are similar to those in previous studies (4-7). On dynamic MRI, they often show a gradual enhancement thought to reflect the significant amount of collagenous tissue and myxoid change of the tumor (5). The enhancement pattern can vary. Certain cases of fibromatosis of the breast were reported to have rapid enhancement and washout on dynamic MRI (type 2 curve), mimicking that of an invasive carcinoma. In such cases, the lack of peripheral ring enhancement, typical for breast cancers, can be a differentiating feature (8). MRI also provides an accurate evaluation of the involvement of the pectoralis major muscle, which is important for surgical planning (5, 8).

Grossly, the appearance of desmoid type fibromatosis can vary from being well-circumscribed nodular lesions to irregular infiltrative lesions. Histologically, the hallmark of a desmoid type fibromatosis is the presence of non-encapsulated bland-looking spindle cells organized into long sweeping and intersecting fascicles with fingerlike extensions at the periphery of the lesion into adjacent the breast parenchyma and adipose tissue (9). In desmoid type fibromatosis, the overall cellularity is low to moderate with no cytologic pleomorphism or increase in mitotic activity, which is important to distinguish it from metaplastic fibrosarcoma. In case of immunohistochemistry, positivity for actin and vimentin is useful for the diagnosis of desmoid type fibromatosis. Desmin is rarely positive, whereas S100 and CD34 are usually negative. β-catenin nuclear staining is also an option for diagnosis, but it may be only focally positive. Meanwhile, cytokeratin staining is helpful in ruling out a carcinoma (1, 9).

Given the local aggressiveness and frequent recurrence, the standard treatment of desmoid type fibromatosis involves a wide surgical resection with clear margins (10). Povoski et al. (11) reported performing repeated excision in a patient because of positive margin from primary surgery. Mastectomy was performed for our patient because of the multicentric lesions and nipple-areolar complex involvement of the disease. Clear margins were obtained.

Desmoid type fibromatosis of the breast is an unusual but distinct entity. Given the patient's young age and familial history of breast cancer, MRI of the breasts is preferred over mammogram since the patient has denser breasts. All clinicians should be aware of this disease entity. Any discordance in clinical, radiological, and pathological assessment for any of the breast cancer symptoms must be further discussed and investigated. Although desmoid tumors have no metastatic potential, its local aggressiveness may be devastating if its treatment is delayed.

Informed Consent: Informed consent was obtained from the patient.

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Author Contributions

Concept: A.V.; M.H.S.; Design: A.V.; M.T.R.; Supervision: A.V; K.R.; Resources: P.J.; M.S.T.; Materials: S.Y.T.; Data Collection and/or Processing: S.Y.T.; Analysis and/or Interpretation: S.Y.T.; W.L.N.; Literature Search: S.Y.T.; Writing Manuscript: S.Y.T.; Critical Review: W.L.N.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Case Report

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Three Cases of Breast Metastases from Lung Cancer and Systematic Review of the Literature

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ABSTRACT

Despite the high prevalence of lung cancer among other primary tumors, metastasis of this particular malignancy in the breast is very rare. We report three new cases of lung cancer with breast metastases and discuss radiological and clinical findings. Radiologically, each case displayed different characteristics. First, one of them had bilateral superficially and deeply located irregular lesions. Second, the patient presented with findings similar to inflammatory breast cancer. The third case had a circumscribed mass, resembling a benign complicated cyst. To guide clinicians for proper patient management, radiologists should be aware of the scope of typical and atypical imaging findings of metastatic involvement of the breast.

Keywords: Breast neoplasm, breast metastasis, lung cancer, breast ultrasound

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Key Points

- Metastatic tumors in the breast have a wide array of radiological manifestations.
- For pathological confirmation, needle biopsy should be performed for interval lesions in a patient with a known history of lung cancer, even with a probably benign appearance.
- Radiologists should be aware of the range of typical and atypical imaging findings of metastatic involvement of the breast to guide clinicians for proper patient management.

Introduction

The incidence of metastatic spread from extramammary sites to the breast varies between 0.4% and 1.3% of all breast malignancies in clinical series (1-6). The breast is considered to be resistant to metastasis because it contains large areas of fibrous tissue with a relatively low supply of blood (7, 8). Most common malignancies that metastasize into the breast are lymphoma, leukemia, and melanoma. Some of the less common primary tumors are carcinomas of the ovary, stomach, and lung, and very rare sources are carcinoid tumors, hypernephromas, and carcinomas of the liver, thyroid, tonsil, pleura, pancreas, cervix, perineum, endometrium, and bladder (7, 9).

It is important to differentiate primary from secondary breast malignancies because therapeutic approaches and outcomes are very different. In the literature, various radiological findings have been described. Moreover, there are few detailed imaging reports of metastatic breast lesions from lung cancer. We report three cases of breast metastases from primary lung cancer, each with different radiological findings. We also present a systematic review of the literature covering all cases published in English until 2019.

Case Presentations

Case 1

A year after she was diagnosed with small-cell lung cancer, a 52-year-old female patient felt a lump in her right breast. The mammograms performed 6 months ago were unremarkable, so the first line of imaging was bilateral whole-breast ultrasound (US). Further, US showed a

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superficially located 9-mm round solid mass with irregular margins and an echogenic halo at 9 o'clock position in the right breast (Figure 1a). On Doppler US imaging, the lesion showed central and peripheral vascularization, which resembled a primary tumor. However, there were two additional irregular Breast Imaging-Reporting and Data System (BIRADS 4) lesions with indistinct margins at 12 o'clock position in the right breast and a well-defined nodule at 9 o'clock position in the left breast. The widths of these lesions, respectively, were 10 mm, 3 mm, and 6 mm. One was superficially located in the subcutaneous fat, and the other two were deep within the parenchyma. One of them was a heterogeneous hyperechoic lesion, and the small lesion had an echogenic rim (Figure 1b). Due to these additional lesions with unusual appearances, the possibility of bilateral breast metastases was considered, and mammography was performed. Mammograms (Figures 2a and 2b) revealed additional small nodules in both breasts with microlobulated and indistinct margins that were not detected in the US.

Tumor infiltration by small-cell carcinoma was demonstrated by ultrasound-guided core needle biopsy of the index lesion (Figure 3). Moreover, immunohistochemical analysis showed tumor cells positive for synaptophysin, chromogranin, and TTF-1. The tumor displayed high Ki-67 (90%) proliferation index.

The patient continued chemotherapy, and magnetic resonance imaging (MRI) (Figures 4a and 4e) of the breast revealed progression in the diameter and number of lesions after 6 months. Almost all of them were hyperintense in fat-saturated T2-weighted images (Figures 4a and 4b). In contrast-enhanced images, most of the lesions showed rim enhancement and type-3 enhancement kinetics (Figures 4c and 4d). On the other hand, in diffusion-weighted images, they showed restricted diffusion (Figure 4e).

Following the development of multiple brain metastases, the patient died 18 months after the diagnosis of primary lung cancer and 6 months after the diagnosis of breast metastases.

Case 2

A 70-year-old female patient who had a strong family history of lung cancer presented with dyspnea. Chest X-ray and consequent computed tomography (CT) scan of the thorax revealed a 26-mm spiculated mass in the anterior segment of the upper lobe of the left lung, followed by bilateral mediastinal and left hilar lymphadenopathies and left pleural effusion. Furthermore, tissue diagnosis of the lung tumor was adenocarcinoma of the lung. Pleural effusion also demonstrated malignant cytology. In addition, brain magnetic resonance imaging (MRI) revealed additional metastatic lesions in the brain and the left frontal bone. For the brain lesion, she received systemic chemotherapy and stereotactic radiotherapy.

Eight months later, positron emission tomography (PET) scan demonstrated left axillary lymphadenopathy as an interval finding. Two months after this finding and 10 months after the diagnosis of her primary tumor, she detected a lump in her left breast. Mammography revealed skin thickening and trabecular thickening in the lower outer quadrant of the left breast (Figure 5a). On the other hand, US revealed subcutaneous tissue edema, parenchymal distortion, and multiple small vertically oriented irregular hypoechoic non-mass lesions in the lower outer quadrant of the left breast, covering an area of approximately 4 cm in diameter (Figure 5b). Further, there was evidence of primary inflammatory breast cancer. Ultrasound-guided core needle biopsy of the lesions was then performed. Moreover, hematoxylin-eosin (H&E) stained paraffin sections of the breast needle biopsy revealed adenocarcinoma (Figure 6a). The tumor cells demonstrated immunoreactivity for TTF-1 and CK7 and negative immunostain with GATA3, estrogen receptor, and progesterone receptor (Figure 6b). The histopathological findings were consistent with metastasis of pulmonary adenocarcinoma and diffuse intralymphatic spread. Mutational analysis of the tumor in the breast core biopsy specimen demonstrated an L858R mutation in Exon 21 of the *EGFR* gene. Later on, the patient died 15 months after diagnosis of primary lung cancer and approximately 7 months after breast metastasis was diagnosed.

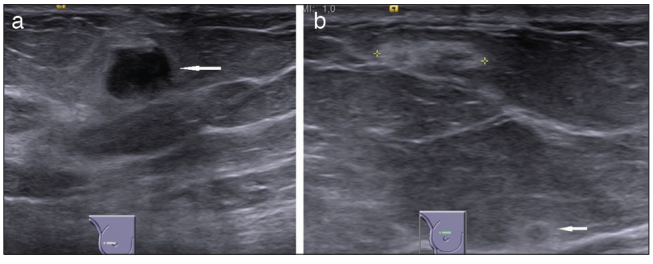

Figure 1. US examination: **(a)** superficially located irregular solid nodular lesion with echogenic halo at 9 o'clock position in the right breast (arrow). **(b)** Hyperechoic lesion (in calipers) and a deeply located heterogeneous nodule with an echogenic halo (arrow) at 12 o'clock position in the right breast

US: Ultrasonography

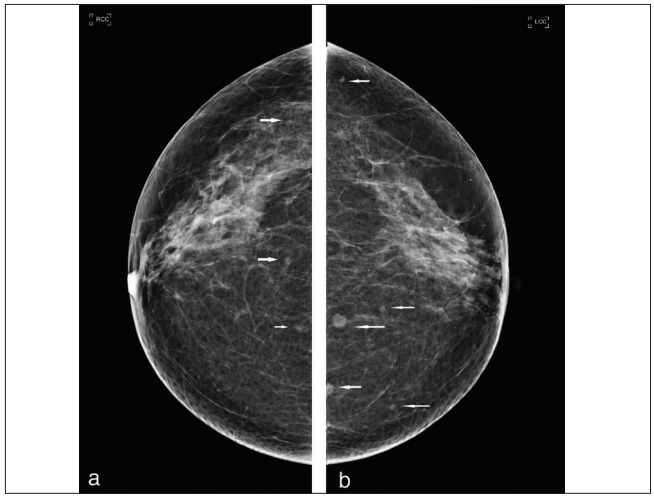

Figure 2. (a,b) Mammography (craniocaudal views) shows multiple nodules smaller than 1 cm with indistinct/microlobulated margins (arrows)

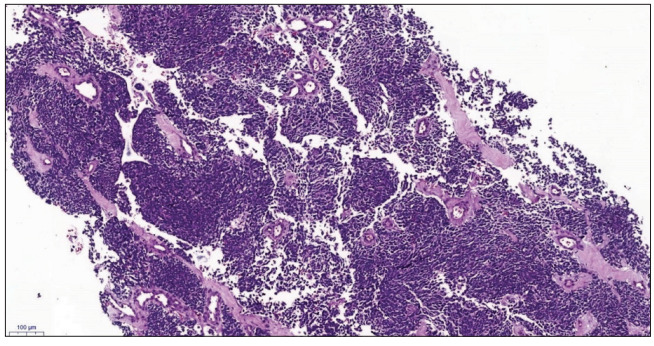

Figure 3. Breast biopsy. Small-cell carcinoma (H&E)

H&E: Hematoxylin-eosin

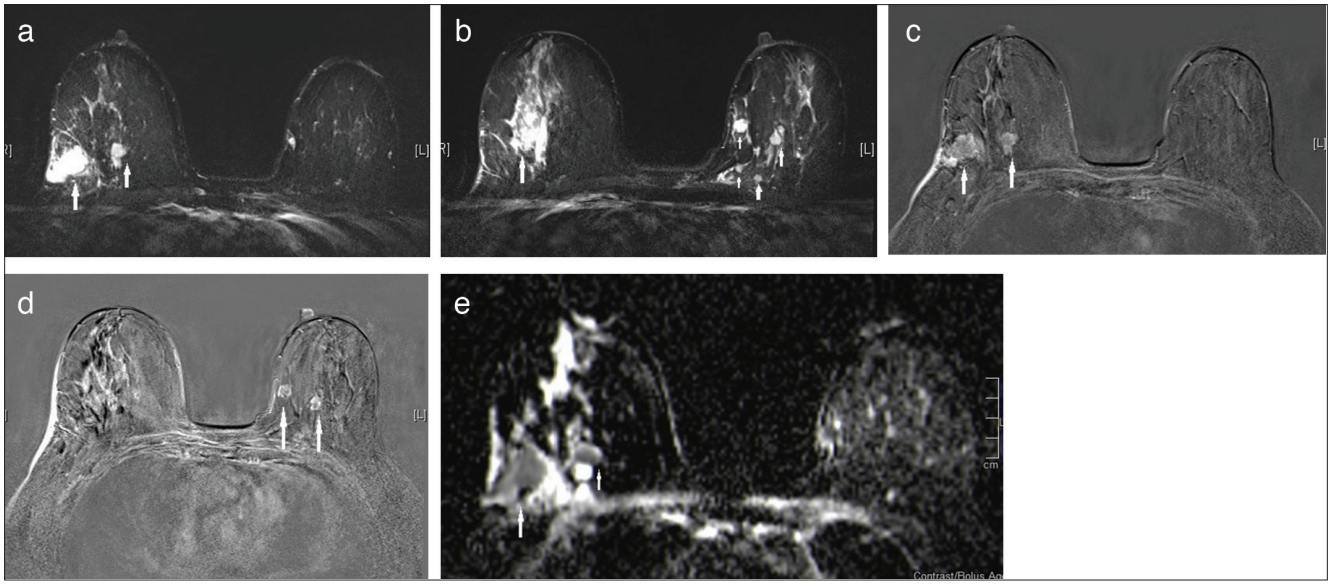

Figure 4. Breast MRI examination. **(a-b)** Fat-saturated T2-weighted images show bilateral multiple irregular hyperintense nodular lesions (arrows). **(c-d)** Contrast-enhanced T1-weighted subtraction images: most of the lesions displayed rim enhancement (arrows). **(e)** Diffusion-weighted images ADC map: lesions showed restricted diffusion (arrows)

MRI: Magnetic resonance imaging; ADC: Apparent diffusion coefficient

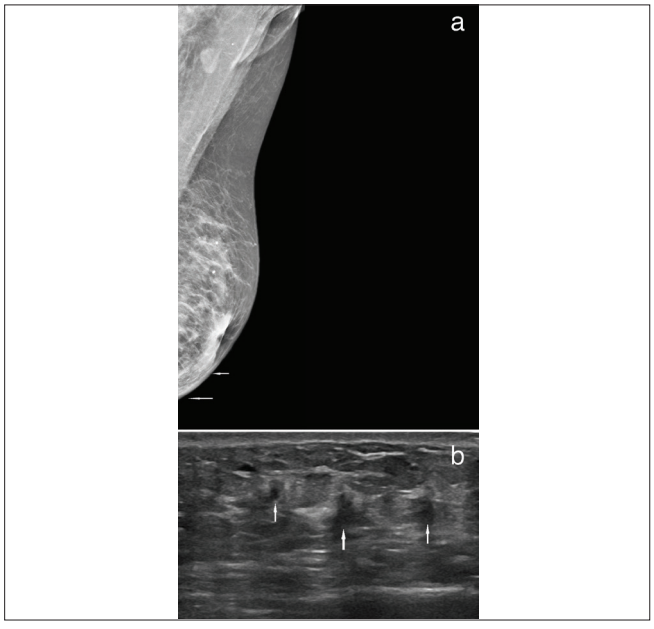

Figure 5. (a) Mammography (left mediolateral oblique view) demonstrates trabecular thickening and skin thickening (arrows) in the lower outer quadrant of the left breast. Retraction of both nipples is noted as incidental finding. **(b)** Ultrasound of the left breast: irregular, vertically oriented, non-mass lesions (arrows) are seen

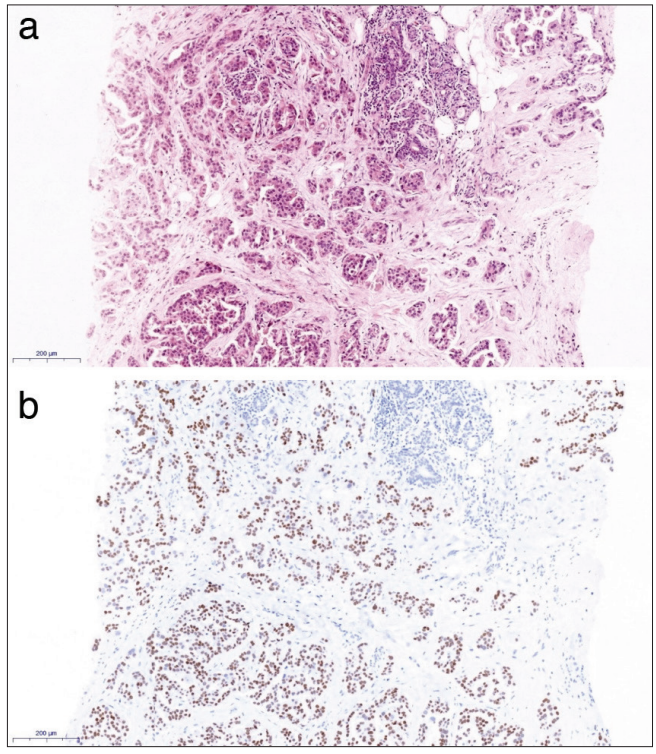

Figure 6. (a) Breast biopsy. Adenocarcinoma (H&E). **(b)** Tumor cells positive with TTF-1 immunostain

H&E: Hematoxylin-eosin

Case 3

A 64-year-old heavy smoker female patient, who had smoked for 40 years and suffered from dyspnea, was diagnosed with a mass in the upper lobe of the left lung. CT scan revealed a centrally located tumor with mediastinal invasion as well as pleural effusion and multiple mediastinal lymphadenopathies. Moreover, the pathological diagnosis was small-cell lung cancer. Ten months after the diagnosis of the primary tumor, a PET scan was performed. In the upper inner quadrant of the left breast, right adrenal metastasis, multiple intraabdominal lymphadenopathies, and hypermetabolic nodular lesion were detected. A bilateral breast US examination was performed, showing an 8-mm circumscribed hypoechoic round lesion at 9 o'clock position in the left breast (Figure 7a). At first examination, it resembled a complicated cyst that displayed no internal vascularization. However, a second examination revealed the solid nature of the nodule and an echogenic halo around it, when

window levels were adjusted (Figure 7b). In addition, US-guided core needle biopsy demonstrated tumor infiltration by small-cell carcinoma (Figure 8). Immunohistochemical analysis showed tumor cells positive for synaptophysin, chromogranin, pan-cytokeratin, and TTF-1. The tumor had a high Ki-67 (95%) proliferation index. Later on, the patient died 26 months after lung cancer was diagnosed and 16 months after the diagnosis of breast metastasis.

Discussion

Breast metastases from extramammary sites are very rare. Lung cancer, which is a common malignancy and one of the leading cancer-related causes of death worldwide, frequently spreads to other organs but metastasizes to the breast very rarely. A few reviews have previously been published on lung cancer metastasizing to the breast (3, 4, 10-13). Alva and Shetty Alva (12) reported 78 cases in their literature review from 1855 to 1998. The most recent and largest review published in 2018 has reported 169 cases from 1999 to 2017 (13). In the cases of Alva and Shetty Alva (12), we have found 180 additional cases of metastatic lung tumors in the breast and made a summary of a total of 258 cases published in English until 2019. Moreover, we could reach the histologic type of lung tumor in 111 cases. Nine of these were identified as non-small-cell lung cancer. The remaining 102 cases were also reported: 61 adenocarcinomas, 14 neuroendocrine tumors, 12 small-cell carcinomas, nine squamous cell carcinomas, two carcinoid tumors, and one each of anaplastic carcinoma, large-cell cancer, pleomorphic carcinoma, and adenosquamous carcinoma.

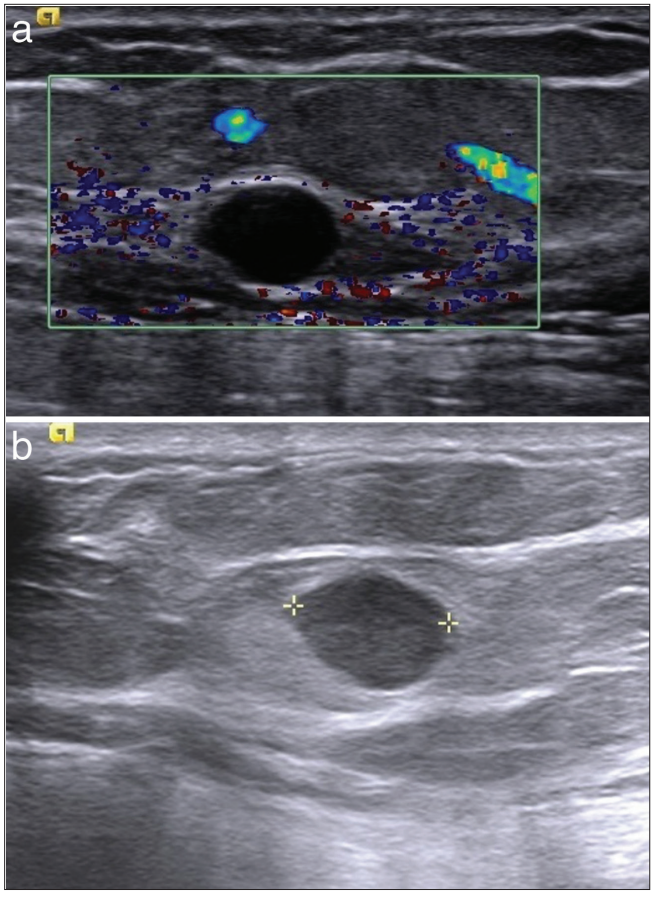

Figure 7. (a) Ultrasound of the left breast: superficially located well-defined cyst-like avascular round lesion. **(b)** Second US examination revealed the solid nature of the nodule and an echogenic halo

US: Ultrasonography

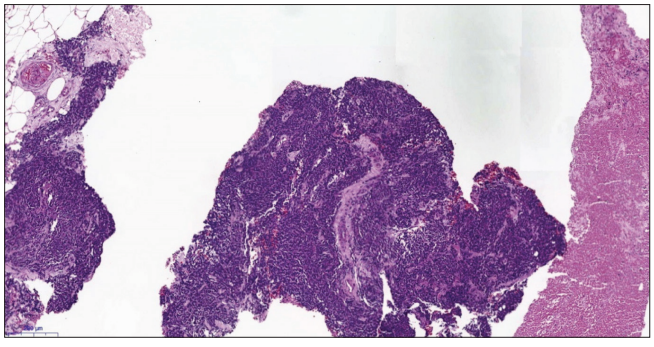

Figure 8. Breast biopsy. Small-cell carcinoma with necrosis (H&E)

H&E: Hematoxylin-eosin

Metastatic tumors in the breast have a wide variety of radiological appearances. Some may mimic a probably benign lesion, whereas some may be similar to primary breast carcinomas (3, 9). Lee et al. (14) also reported that only 2 were classified as BIRADS 3 in their series of 33 cases of breast metastases, the rest being categorized as BIRADS 4b or higher. They are usually unilateral and unifocal with a predilection for the upper outer quadrant, but it has been reported that around 33% can be multifocal and 15% can be bilateral (15). The most common radiological appearance is a round or oval mass with uncircumscribed margins located superficially in the subcutaneous tissue (10). Lee et al. (16) have stated that around 75% of cases have irregular margins. Superficial location can be an indication, as primary cancers that arise from the ductal or lobular tissue tend to be deeply located in the parenchyma (1). Although superficially located, unlike primary masses, they do not cause skin or nipple retraction. In secondary tumors, spiculation, posterior shadowing, and calcifications usually detected in primary breast cancers are very rare (2, 3, 7, 16). Calcifications have been identified in metastases of ovarian, gastric, thyroid, and mucin-producing gastrointestinal cancers (14). Metastatic lesions tend to develop rapidly and lack desmoplastic response, which is a typical finding of primary breast cancer (9). Therefore, contrary to primary tumors, an echogenic halo around the mass and parenchymal distortion is not typical characteristics of breast metastases. Nevertheless, two of our cases had an echogenic halo. Moreover, the differential diagnosis of benign and malignant lesions is made easier by the echogenic halo. In case number three, it was evident only after the window level was adjusted, which highlights the significance of meticulous imaging. Echo patterns of metastatic lesions can be homogeneous or heterogeneous (7). Masses may contain cystic areas due to hemorrhage or necrosis. This is more frequently detected in lymphoproliferative lesions as well as gastric, hepatocellular, and ovarian cancers (17). Due to high cellular proliferation, metastatic tumors may also present with a pseudocystic appearance at US. Thus, they may resemble complicated cysts as in one of our cases or triple-negative breast carcinomas (9). As seen in the third case, radiologists should be very cautious before calling these lesions cysts, especially in patients with primary malignancies. Color Doppler US imaging may also be helpful in differentiation.

There are very few studies in the literature on MRI findings for breast metastases. As in the first case, metastatic lesions mostly demonstrate rim enhancement, type-3 enhancement curve, and restricted diffusion on breast MRI, clearly indicating their malignant nature (17). Depending on the presence of necrosis, they can be hypo- or hyperechoic on T2-weighted images. In their series of breast metastases, Mun et al. (9)

have also defined some atypical imaging features, such as non-mass lesions and segmentally or ductally distributed micronodules, similar to the results in our second case.

Depending on the route of disease transmission, clinical and radiological findings of breast metastases may vary (4, 10, 16-18). Hematologically disseminated lesions tend to appear as single or multiple, round to oval, circumscribed, or irregular masses commonly superficially located in subcutaneous tissue or immediately adjacent to the breast parenchyma, which is relatively rich in blood supply (9, 16). Furthermore, axilla is less commonly involved (9). Our first case represents a good example. There were multiple lesions superficially located in the subcutaneous fatty tissue and additional lesions deep in the parenchyma. Tumors that spread through the lymphatic route tend to manifest in the subcutaneous lymphatic channels as skin thickening, subcutaneous edema, and trabecular thickening due to tumor emboli (2). An apparent mass may or may not be present (9, 17). Mammography usually indicates asymmetric opacity, and MRI may demonstrate non-mass enhancement and edema. Clinically, peau d'orange and redness on the skin may occasionally be observed. These cases can be falsely diagnosed as mastitis or inflammatory breast cancers (2, 4). It has been documented that ovarian, gastric, and lung cancers lead to this type of breast metastases (4, 16, 19, 20). Huang et al. (11) reported that pleural effusion, pleural thickening, and ipsilateral axillary lymphadenopathy precede the development of breast lesions in lung cancers that spread through the lymphatic route to the breast. They have also indicated that the breast is affected in a retrograde fashion after the intervention of the axilla. In our second case, radiological findings are probably consistent with this type of dissemination. In lung cancer patients with pleural effusion, the axilla and the breast should be closely examined. Another means of spreading lung cancer to the breast can be through direct chest wall invasion, but this is not a common finding.

There are no specific predisposing factors associated with breast metastases. It has been postulated that by increasing the vascularity of the breast, estrogen may have a role as a predisposing factor in the development of metastasis. This has been proposed as an explanation for the relatively higher incidence of breast metastases in young women (9, 16). In contradiction to this hypothesis, all of our patients were postmenopausal women. Clinically, the presenting symptom was palpable breast lump in two of our three cases in accordance with the literature (2). In one case, the breast mass was an incidental finding in the PET-CT.

In conclusion, breast metastases from lung cancer are very rare, but it is clinically very important to distinguish primary from metastatic breast lesions. It is also important to apply the necessary chemotherapeutic regimens for metastatic patients and to guide them correctly in their disease prognosis while avoiding unnecessary surgical treatments. In this article, we present a literature review as well as three new cases, each with distinct radiological appearances. These cases support other studies of breast metastases, demonstrating a variety of radiological findings. Due to the lack of specific radiological features, immunohistochemical studies are important to reach an accurate diagnosis.

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