



E-ISSN 2149-1976

[www.thejournalofbreasthealth.com](http://www.thejournalofbreasthealth.com)

# The Journal of Breast Health

VOLUME: 12 • ISSUE: 1 • JANUARY 2016

## Clinical Oncology Study Group Report

Vahit Özmen et al; *İstanbul, Ankara, Sakarya, Turkey; Köln, Germany; Florida, Pittsburgh, USA; UK*

## Health Beliefs and Breast Cancer Screening

Meryem Yılmaz and Tuğba Durmuş; *Sivas, Turkey*

## MR Guided Breast Biopsies

Fahrettin Kılıç et al.; *İstanbul, Diyarbakır, Turkey*

## Breast Cancer Related Lymphedema Risk Factors

Aslı Gençay Can et al.; *Ankara, Turkey*

## Sonoelastography in Breast Masses

Adile Balçık et al.; *Afyonkarahisar, Samsun, Turkey*

Editor-in Chief

**Vahit ÖZMEN, Turkey**

International Editor

**Atilla SORAN, USA**

# The Journal of Breast Health

The Journal of Breast Health is the official journal of the  
**TURKISH FEDERATION OF BREAST DISEASES  
ASSOCIATIONS.**



**MHDF**

OWNER AND  
RESPONSIBLE MANAGER  
**Dr. Vahit Özmen**  
On Behalf of the **TURKISH FEDERATION  
OF BREAST DISEASES ASSOCIATIONS.**

Contact  
Department of General Surgery,  
İstanbul University İstanbul Medical Faculty,  
C Service Çapa / İstanbul  
Phone&Fax : + 90 212 534 02 10

Editor

**Vahit Özmen**

*İstanbul University İstanbul Medical Faculty, İstanbul, Turkey*

International Editor

**Atilla Soran**

*University of Pittsburgh, Magee-Womens Hospital, Pittsburgh, PA, USA*

Associate Editors

**Erkin Arıbal**

*Marmara University Faculty of Medicine, İstanbul, Turkey*

**Nilüfer Güler**

*Hacettepe University Faculty of Medicine, Ankara, Turkey*

**Seher Demirer**

*Ankara University Faculty of Medicine, Ankara Turkey*

**Hale Başak Öztürk Çağlar**

*Medipol University Faculty of Medicine, İstanbul, Turkey*

**Gürsel Soybir**

*Namık Kemal University Faculty of Medicine, Tekirdağ, Turkey*

Assistant Editors

**Ayfer Kamalı Polat**

*Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey*

Biostatistics Editor

**Birol Topçu**

*Namık Kemal University Faculty of Medicine, Tekirdağ, Turkey*

Medical English Advisor

**Didem Öncel Yakar**

The Journal of Breast Health is indexed in Index Copernicus, EBSCO,  
TÜBİTAK ULAKBİM Medical Databases, Türk Medline and Turkish Citation Index databases.



Publisher  
**İbrahim KARA**

Publication Director  
**Ali ŞAHİN**

Deputy Publication Directors  
**Gökhan ÇİMEN**  
**Dişad GÜNEY**

Publication Coordinators  
**Ebru MUTLU**  
**Esra GÖRGÜLÜ**

**Betül ÇİMEN**  
**Nihan GÜLTAN**  
**Zeynep YAKIŞIRER**  
Finance Coordinator  
**Veynel KARA**

Project Coordinator  
**Hakan ERTEN**

Project Assistants  
**Büşra KALKAN**  
**Duygunur CAN**

Graphics Department  
**Ünal ÖZER**  
**Neslihan YAMAN**  
**Kübra ÇOLAK**

Contact

Address : Büyükdere Cad. No: 105/9 34394  
Mecidiyeköy, Şişli, İstanbul, Turkey

Phone : +90 212 217 17 00

Fax : +90 212 217 22 92

E-mail : info@avesyayincilik.com

## National Editorial Board

### **Bülent Alıç**

*Ankara University Faculty of Medicine, Ankara, Turkey*

### **Varol Çelik**

*İstanbul University Cerrahpaşa Faculty of Medicine,  
İstanbul, Turkey*

### **Serdar Özbaş**

*Ankara Güven Hospital, Ankara, Turkey*

### **Füsun Taşkın**

*Adnan Menderes University Faculty of Medicine,  
Aydın, Turkey*

### **Neslihan Cabioğlu**

*İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey*

### **Yeşim Eralp**

*İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey*

### **Zerrin Calay**

*İstanbul University Cerrahpaşa Faculty of Medicine,  
İstanbul, Turkey*

### **Ertuğrul Gazioğlu**

*İstanbul University Cerrahpaşa Faculty of Medicine,  
İstanbul, Turkey*

### **Kemal Atahan**

*İzmir Katip Çelebi University Atatürk Education and  
Research Hospital, İzmir, Turkey*

### **Ercüment Tarcan**

*İzmir Katip Çelebi University Atatürk Education and  
Research Hospital, İzmir, Turkey*

## International Editorial Board

*(Co-Editor for International Review Board: Atilla Soran MD, Pittsburgh, USA)*

### **Gretchen Ahrendt**

*University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*

### **Stanley N C Anyanwu**

*Nnamdi Azikiwe University, Teaching Hospital,  
Nnewi, Nigeria*

### **Tayanç Öncel**

*Mamer Surgical Center, Bursa, Turkey*

### **Türkkan Evrensel**

*Uludağ University, Faculty of Medicine, Bursa, Turkey*

### **Berna Öksüzoğlu**

*Dr. Abdurrahman Yurtaslan Ankara Oncology Education  
and Research Hospital, Ankara, Turkey*

### **Zafer Utkan**

*Kocaeli University Faculty of Medicine, Kocaeli, Turkey*

### **Sadullah Girgin**

*Dicle University, Faculty of Medicine, Diyarbakır, Turkey*

### **Durmuş Etiz**

*Osmangazi University Faculty of Medicine, Eskişehir, Turkey*

### **Alper Akcan**

*Erciyes University Faculty of Medicine, Kayseri, Turkey*

### **Gürhan Sakman**

*Çukurova University Faculty of Medicine, Balcalı Hospital,  
Adana, Turkey*

### **Şahande Elagöz**

*Sivas Cumhuriyet University Faculty of Medicine,  
Sivas, Turkey*

### **Yamaç Erhan**

*Celal Bayar University Faculty of Medicine, Manisa, Turkey*

### **Banu Arun**

*The University of Texas MD Anderson Cancer Center,  
Houston, TX, USA*

### **Sushil Beriwal**

*University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*

**Funda Meriç Bernstam**

*The University of Texas MD Anderson Cancer Center,  
Houston, TX, USA*

**Jose L.B. Bevilacqua**

*University of São Paulo Faculty of Medicine, São Paulo,  
Brazil*

**Marguerite Bonaventura**

*University of Pittsburgh School of Medicine, Pittsburgh,  
PA, USA*

**Patrick Borgen**

*Maimonides Medical Center, New York, NY, USA*

**Mihail Coculescu**

*University of Medicine and Pharmacy Carol Davila,  
Bucharest, Romania*

**Ivan Drinkovic**

*Hrvatsko Senolosko Drustvo HLZ-a KB Merkur,  
Zagreb, Croatia*

**Jeffrey Falk**

*St. John Hospital and Medical Center, Detroit, MI, USA*

**Eisuke Fukuma**

*Breast Center, Kameda Medical Center, Kamogawa, Chiba, Japan*

**Kevin S. Hughes**

*Harvard Medical School, Boston, MA, USA*

**Lidija Lincender**

*Emeritus Professor, Sarajevo, Bosnia-Herzegovina*

**Barry Lembersky**

*University of Pittsburgh School of Medicine, Pittsburgh,  
PA, USA*

**Ronald Johnson**

*University of Pittsburgh, Magee-Womens Hospital,  
Pittsburgh, PA, USA*

**Kandace McGuire**

*University of Pittsburgh, Magee-Womens Hospital,  
Pittsburgh, PA, USA*

**Lydia Mouzaka**

*University of Athens School of Medicine, Athens, Greece*

**Lisa A. Newman**

*University of Michigan, Comprehensive Cancer Center,  
Michigan, USA*

**Masakuna Noguchi**

*Kanazawa University School of Medicine, Kanazawa, Japan*

**Se-Jeong Oh**

*The Catholic University of Korea College of Medicine,  
Seoul, Korea*

**Tadeusz Pienkowski**

*Medical University of Gdansk, Gdansk, Poland*

**Antonio Pinero**

*Virgen de la Arrixaca University Hospital, Murcia, Spain*

**Dimitrios H. Roukos**

*Ioannina University School of Medicine, Ioannina, Greece*

**Miguel Oller Sanz**

*Clínica Abreu, Santo Domingo, Dominican Republic*

**Barbara Lynn Smith**

*Massachusetts General Hospital, Boston, MA, USA*

**Jules Sumkin**

*University of Pittsburgh School of Medicine, Pittsburgh,  
PA, USA*

**Ayşegül Şahin**

*The University of Texas MD Anderson Cancer Center,  
Houston, TX, USA*

**Jorge A. Toro**

*University of Pittsburgh, Magee-Womens Hospital,  
Pittsburgh, PA, USA*

**Vincent Vinh-Hung**

*University Hospitals of Geneva, University of Geneva,  
Geneva, Switzerland*

**M. Firdos Ziauddin**

*University of Pittsburgh Medical Center, Pittsburgh, PA, USA*

## Aims and Scope

The Journal of Breast Health is the open access, scientific online-only publication organ of the Turkish Federation of Breast Diseases Societies that is published in accordance with independent, unbiased, double blind peer review principles. (The journal, which was established in 2005 under the title of Meme Sağlığı Dergisi / The Journal of Breast Health, has been published under the title of The Journal of Breast Health (J Breast Health) as an online-only publication since April 2014)

The publication language of the journal is both in Turkish and English, and it is published quarterly on January, April, July and October.

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

The editorial policies and publication process are implemented in accordance with rules set by the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), European Association of Science Editors (EASE), Committee on Publication Ethics (COPE), and the Heart Group.

The Journal of Breast Health is indexed in EBSCO, Index Copernicus, DOAJ, TUBITAK ULAKBIM TR Index and Turkish Citation Index.

All manuscripts must be submitted via the online submission system which is available through the journal's web page at [www.thejournalofbreasthealth.com](http://www.thejournalofbreasthealth.com).

The journal's guidelines, technical informations and the required forms are available in the journal's web page.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Turkish Federation of Breast Diseases Societies, the editors, the editorial board and/or the publisher; the editors, the editorial board and the publisher disclaim any responsibility or liability for such materials.

All published content is available online free of charge at [www.thejournalofbreasthealth.com](http://www.thejournalofbreasthealth.com).

National and international copyrights of the published content belongs to the Turkish Federation of Breast Diseases Societies. Other than providing reference to scientific material, permission should be obtained from the Turkish Federation of Breast Diseases Societies for electronic submission, printing, distribution, any kind of reproduction and reutilization of the materials in electronic format or as printed media:

Editor: Prof. Dr. Vahit ÖZMEN

Address: İstanbul Üniversitesi, İstanbul Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Çapa, İstanbul

Phone: +90 (212) 534 02 10

Fax: +90 (212) 534 02 10

E-mail: [editor@thejournalofbreasthealth.com](mailto:editor@thejournalofbreasthealth.com)

Web: [www.thejournalofbreasthealth.com](http://www.thejournalofbreasthealth.com)

Publisher: AVES - İbrahim KARA

Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey

Phone: +90 (212) 217 17 00

Fax: +90 (212) 217 22 92

E-mail: [info@avesyayincilik.com](mailto:info@avesyayincilik.com)

The Journal of Breast Health is an international periodical that is published in an electronic format in accordance with the principles of independent, unbiased, and double-blinded peer-review. Four issues are published annually; in January, April, July and October.

A print version of the journal is not available and it is only accessible at the website [www.thejournalofbreasthealth.com](http://www.thejournalofbreasthealth.com). The manuscripts on this web page can be accessed free of charge, and full text PDF files can be downloaded.

Authors should submit manuscripts through the journal website ([www.thejournalofbreasthealth.com](http://www.thejournalofbreasthealth.com)). Manuscripts sent by other means will not be evaluated. Full text of the manuscripts may be in either Turkish or English. The title, abstract and keywords in every manuscript should be written in both Turkish and English. However, foreign authors outside of Turkey are not required to include the Turkish title, abstract and keywords during their manuscript submission.

Preliminary conditions for the approval of a manuscript include originality, having a high scientific value and citation potential.

Submitted manuscripts should not have been presented or published elsewhere in either electronic or printed format. A statement should be included for previous submission to and rejection by another journal. Relaying previous reviewer evaluation reports would accelerate the evaluation process. Name, date and place of the event must be specified if the study has been previously presented at a meeting.

The authors are requested to transfer all copyrights of the manuscript to the journal as of the evaluation process in relevance to the national and international regulations. The Copyright Transfer Form signed by all authors should be submitted to the journal while uploading the manuscript through the system. All financial liability and legal responsibilities associated with the copyright of the contained text, table, figure, picture, and all other sorts of content that are protected by national and international laws belong solely to the author.

The corresponding author is required to complete the Author Contribution Form in order to protect authors' rights, and avoid ghost and honorary authorship issues.

All kinds of aids and support received from both persons and institutions should be declared, and the ICMJE Uniform Disclosure Form for Potential Conflicts of Interest should be completed to clarify conflict of interest issues.

The format of the manuscripts must conform to the journal's instructions and to the standards of ICMJE-Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (updated in December 2014 -<http://www.icmje.org/icmje-recommendations.pdf>), and the presentation of the content must be in accordance with appropriate international guidelines. CONSORT guidelines should be used for the reporting of randomized trials, STROBE for observational studies, STARD for diagnostic studies, PRISMA for systematic reviews and meta-analyses, ARRIVE for animal studies, and TREND for non-randomized behavior and public health intervention studies.

An ethics committee report prepared in accordance with "WMA Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects" and "Guide for the Care and Use of Laboratory Animals" is required for experimental and clinical studies, drug investigations and some case reports. The authors may be asked to submit ethics committee report or a substitute official report, if deemed necessary. In papers reporting the results of experimental studies, a statement should be included in the text indicating that all subjects provided consent for the study, after detailed explanation of all procedures that the volunteer subjects and patients were subjected to. In animal studies, the means of pain and discomfort relief should be clearly specified. Informed consents, name of the ethics committee, issue number and date of the approval document should be written in the Material and Methods section of the main document.

All manuscripts are subject to preliminary evaluation by the Editors. The manuscripts are reviewed for possible plagiarism, replication and duplicated publication during this process. Our journal will impose sanctions in accordance with the

guidelines of Committee on Publication Ethics (COPE) in conditions where such non-ethical issues may arise. Subsequently, manuscripts are forwarded to at least 2 independent referees for double-blinded peer-review. The reviewers are selected among independent experts who have international publications and citations relevant to the subject of the manuscript. Additionally, a statistician evaluates research articles, systematic reviews and meta-analyses. Authors are deemed to have accepted that required revisions are to be made by the Editors provided that this will not make a comprehensive change in the original document.

Upon approval of the manuscript for publication, requests of addition to or removal from the author list or order change will not be accepted.

The manuscripts should be prepared in the form of a Microsoft Office Word document and should comply with the following specifications.

**Original Research:** The abstract should be written in both Turkish and English, and be structured with Objective, Material and Methods, Results and Conclusion sections. The abstract should not exceed 250 words. Keywords must conform to Medical Subject Headings (MeSH) terms prepared by National Library of Medicine (NLM), and contain minimum 3 and maximum 6 items; keywords should be written in both Turkish and English just below the abstract. The main text should contain Introduction, Material and Methods, Results, Discussion and Conclusion sections, References, Tables, Figures and Images, and should be limited to 5000 words excluding references. The number of references should be limited to 50.

Statistical analyses must be conducted in accordance with the 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). Statistical analyses should be written as a subheading under the Material and Methods section and the statistical software used must certainly be specified. Data must be expressed as mean  $\pm$  standard deviation when parametric tests are used to compare continuous variables, and as median (minimum-maximum) and percentiles (25<sup>th</sup> and 75<sup>th</sup> percentiles) when non-parametric tests are used. In advanced and complicated statistical analyses, relative risk (RR), odds ratio (OR) and hazard ratio (HR) must be supported by confidence intervals (CI) and p values.

**Editorial Comments:** Editorial comments aim at providing brief critical commentary by the reviewers having expertise or with high reputation on the topic of the research article published in the journal. Authors are selected and invited by the journal. Abstract, Keywords, Tables, Figures, Images and other media are not included. The main text should not include subheadings and be limited to maximum 1500 words; references should be limited to 15.

**Review:** Reviews that are prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications and higher citation potential are taken under review. The authors may be invited by the journal. Reviews should be describing, discussing and evaluating the current level of knowledge on a topic used in clinical practice and should guide future studies. The manuscript should contain an unstructured abstract not exceeding 250 words, and should include minimum 3 and maximum 6 keywords which conform to Medical Subject Headings (MeSH) terms prepared by National Library of Medicine (NLM). The main text should not exceed 5000 words and the references should be limited to 50.

The originality of the visual media contained in the reviews should be confirmed by submitting a letter to the journal. The original versions of the printed or electronic copies of the images adapted from a published source should be cited properly and the written permission obtained from the copyright holder (publisher, journal or authors) should be forwarded to the journal.

**Case Report:** Only a limited number of case reports are published in the journal. Reports on rare cases or conditions that constitute challenges in the diagnosis and treatment, those offering new therapies or revealing knowledge not included in textbooks, and interesting and educative case reports are accepted for publication. The abstract should be unstructured and should not exceed 250 words. The

## Instructions to Authors

manuscript should include minimum 3 and maximum 6 keywords which conform to Medical Subject Headings (MeSH) (<https://www.nlm.nih.gov/mesh/MBrowser.html>) terms prepared by National Library of Medicine (NLM). The text should include Introduction, Case Report, Discussion and Conclusion sections, References, Tables, Figures and Images, and should be limited to 700 words. References should be limited to 10.

**Letter to the Editor:** Includes manuscripts discussing important parts, overlooked aspects or lacking parts of a previously published article. Articles on the subjects within the scope of the journal that might attract the readers' attention, particularly educative cases can also be submitted in the form of "Letter to the Editor". Readers can also present their comments on the published manuscripts in the form of "Letter to the Editor". Abstract, Keywords, Tables, Figures, Images and other media are not included. The text should be unstructured and should not exceed 500 words; references are limited to 5. The volume, year, issue, page numbers, and title of the manuscript being commented on, as well as the name of the authors should be clearly specified, should be listed in the references and cited within the text.

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

### Special Considerations

Names of the corresponding author and other authors, affiliations, and other information on the study centers should not be included in any part of the manuscript or images in order to allow double-blinded peer-review. Such information should be uploaded to the relevant section of the online submission system, and be separately specified in the title page.

All tables, figures, graphs and other visual media must be numbered in order of citation within the text and must not disclose the names of the patients, doctors or institutions. Tables must be prepared in a Microsoft Office Word document using "Insert Table" command and be placed at the end of the references section in the main document. Tables should not be submitted in JPEG, TIFF or other visual formats. In microscopic images, magnification and staining techniques must be specified in addition to figure captions. All images should be in high resolution with minimum 300 dpi. The lines within the graphs must be in adequate thickness so that loss of details would be minimal if a reduction is needed during press. The width must be either 9 cm or 18 cm. It would be more appropriate if professionals prepare the drawings. Gray color should be avoided. Abbreviations must be explained in alphabetical order at the bottom. Roman numerals should be avoided while numbering the Tables and Figures, or while citing the tables in the text. Decimal points in the text, tables and figures should be separated by comma in Turkish sections and by dots in English sections. Particularly, tables should be explanatory for the text and should not duplicate the data given in the text.

Pharmaceuticals should be specified with their generic names, and medical products and devices should be identified with brand name and company name, city and country.

### References

References should be numbered consecutively within the main text in the order they are cited and should be stated in parenthesis. Only published data or manuscripts accepted for publication and recent data should be included. Inaccessible data sources and those not indexed in any database should be omitted. Titles of journals should be abbreviated in accordance with Index Medicus-NLM Style (Patris K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of

Medicine (US); 2007 - [updated 2011 Sep 15; cited Year Month Day] (<http://www.nlm.nih.gov/citingmedicine>). All authors should be listed if an article has six or less authors; it should not be represented by "et al." in Turkish articles and by "et al." in English articles. References published in PubMed should have a PMID:xxxxxx at the end of it, which should be stated in parenthesis. The reference format and punctuation should be as stated in the following examples:

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

Book Section: Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, editors. *Cardiovascular Medicine*. St Louis: Mosby; 1974.p.273-85.

Books with Single Author: Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Marcel Dekker; 1993.

Editor(s) as author: Norman IJ, Redfern SJ, editors. *Mental health care for elderly people*. New York: Churchill Livingstone; 1996.

Conference Proceedings: Bengissou 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.p.1561-5.

Scientific or Technical Report: Smith P, Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: 1994 Oct. Report No: HHSIGOE 169200860.

Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (dissertation). St. Louis (MO): Washington Univ. 1995.

Manuscripts accepted for publication, but not published: Leshner AI. Molecular mechanisms of cocaine addiction. *N Engl J Med* In press 1997.

Epub ahead of print Articles: Aksu HU, Ertürk M, Gül M, Uslu N. Successful treatment of a patient with pulmonary embolism and biatrial thrombus. *Anadolu Kardiyol Derg* 2012 Dec 26. doi: 10.5152/akd.2013.062. [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/ncidod/EID/cid.htm>.

The latest status of the submitted manuscripts and other information about the journal can be accessed at [www.thejournalofbreasthealth.com](http://www.thejournalofbreasthealth.com). Should you have additional questions, contact details of the Editorial Office and Publisher are provided below for correspondence.

Editor: Prof. Dr. Vahit ÖZMEN

Address: Department of General Surgery, İstanbul University İstanbul Faculty of Medicine, Çapa, İstanbul

Phone: +90 (212) 534 02 10

Fax: +90 (212) 534 02 10

E-mail: [editor@thejournalofbreasthealth.com](mailto:editor@thejournalofbreasthealth.com)

Web: [www.thejournalofbreasthealth.com](http://www.thejournalofbreasthealth.com)

Publisher: AVES - İbrahim KARA

Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey

Phone: +90 (212) 217 17 00

Fax: +90 (212) 217 22 92

E-mail: [info@avesyayincilik.com](mailto:info@avesyayincilik.com)

### REVIEW

- 1** Male Breast Cancer  
Metin Yalaza, Aydın İnan, Mikdat Bozer

### ORIGINAL ARTICLES

- 9** Turkish Ministry of Health, 2<sup>nd</sup> Turkish Medical General Assembly Clinical Oncology Study Group Report  
Vahit Özmen, Nergiz Dağoğlu, İsmet Dede, Adem Akçakaya, Mustafa Kerem, Fatih Göksel, Enver Özgür, Emel Başkan, Mustafa Yaylacı, Adil Ceydeli, Meltem Baykara, Huriye Şenay Kızıltan, Şeref Kömürcü, Mahmut Gümüş, H. Mehmet Türk, Recep Demirhan, Ali Akgün, Naim Kadoglou, Emre Yatman, Cem Cuneit Elbi, Seza Güleç, Atilla Soran, Ahmet Özet, Fahrettin Keleştimur
- 18** Health Beliefs and Breast Cancer Screening Behavior among a Group of Female Health Professionals in Turkey  
Meryem Yılmaz, Tuğba Durmuş
- 25** Magnetic Resonance Imaging Guided Vacuum Assisted and Core Needle Biopsies  
Fahrettin Kılıç, Abdulkadir Eren, Necmettin Tunç, Mehmet Velidedeoğlu, Selim Bakan, Fatih Aydoğan, Varol Çelik, Ertuğrul Gazioğlu, Mehmet Halit Yılmaz
- 31** Assessment of Risk Factors in Patients who presented to the Outpatient Clinic for Breast Cancer-Related Lymphedema  
Aslı Gençay Can, Emel Ekşioğlu, Zeynep Tuba Bahtiyarca, Fatma Aytül Çakıcı
- 37** Efficacy of Sonoelastography in Distinguishing Benign from Malignant Breast Masses  
Adile Balçık, Ahmet Veysel Polat, İlkay Koray Bayrak, Ayfer Kamalı Polat

### CASE REPORTS

- 44** A Rare Breast Tumor: Dermatofibrosarcoma Protuberans  
Tevhide Bilgen Özcan, Ezgi Hacıhasanoğlu, Mehmet Ali Nazlı, Şefika Aksoy, Cem Leblebici, Canan Kelten Talu
- 47** Metaplastic Breast Cancer  
Halil Türkan, M. Şehsuvar Gökgöz, N. Serhat Parlak

### LETTER TO THE EDITOR

- 50** Unknown Effects of Breast Enhancer Products on Diagnostic Imaging Outcomes  
Stefano Pacifici, Miguel Angel De La Camara Egea, Amaia Soria Ibarra

# Male Breast Cancer

Metin Yalaza<sup>1</sup>, Aydın İnan<sup>2</sup>, Mikdat Bozer<sup>3</sup>

<sup>1</sup>Clinic of Surgical Oncology, Konya Training and Research Hospital, Konya, Turkey

<sup>2</sup>Department of General Surgery, Turgut Özal University Faculty of Medicine, Ankara, Turkey

<sup>3</sup>Department of General Surgery, Division of Surgical Oncology, Fatih University Faculty of Medicine, İstanbul, Turkey

## ABSTRACT

Male breast cancer (MBC) is a rare disease, accounting for less than 1% of all breast cancer diagnoses worldwide. Although breast carcinomas share certain characteristics in both genders, there are notable differences. Most studies on men with breast cancer are very small. Thus, most data on male breast cancer are derived from studies on females. However, when a number of these small studies are grouped together, we can learn more from them. This review emphasizes the incidence, etiology, clinical features, diagnosis, treatment, pathology, survival, and prognostic factors related to MBC.

**Keywords:** Breast cancer, male gender, review

## Introduction

Over the past two decades, major improvements have been achieved in the understanding of breast cancer, and cure can be offered if the disease is diagnosed at an early stage. However, the disease is more often diagnosed at more advanced stages (3 or 4) in men, in contrast to women. Its rarity among men as well as lack of awareness leads to its detection at later stages. Randomized studies cannot be carried on due to the low incidence of breast cancer in males, with only a few published prospective therapeutic studies in the literature. While the information on male breast cancer (MBC) was obtained from retrospective studies, the recommendations for treatment were derived from studies conducted on female breast cancer (1). This review presents the frequency, etiology, clinical-pathological characteristics and treatment approaches for the rare MBC.

## Epidemiology-Etiology

Male breast cancer is rare and constitutes 0.5-1% of all patients with breast cancer. The reason of the low incidence rate in men is the relatively low amount of breast tissue along with the difference in their hormonal environment. Even though breast tissue is less in men as compared to women, the factors that influence malignant changes are similar. The Surveillance, Epidemiology and End Result (SEER) Program reported that the incidence of breast cancer was highest at ages 52-71 during 1973-2000, whereas the peak incidence in males was 71 years (2). In fact, some authors state that MBC imitate the behavioral pattern of post-menopausal female breast cancer. The incidence of breast cancer in males and females has increased in the past 25 years. International Association of Cancer Registries (IACR) emphasized this increase and stated that the incidence of female breast cancer increased by 20%, while breast cancer-related deaths increased by 14%. The SEER data also showed that the rate that was 1.1 for 100.000 men in the mid-1970s and raised to 1.44 for 100.000 men by 2010 (3). In USA, 2240 men were diagnosed with breast cancer within the year 2013. The lifetime rate of diagnosis with male breast cancer is 1 in 1000. According to the IACR Turkey data, 0.37% of all cancer types among males are breast cancer (4, 5). IACR has published its new cancer estimates for the year 2012. The most recent cancer estimates for 28 cancer types in 184 countries, which record cancer data, have been made available for users on the GLOBOCAN 2012 website (6).

The rate of presentation with advanced stage breast cancer has been decreasing in men. As a matter of fact, a study conducted in 1995 reported the rate of Stage 1-2 disease on diagnosis as 70%, whereas it was reported as 67% in 2010 and 82% in 2015 (7-9). MBC constitutes less than 1% of male cancers and it has a varying rate of incidence across different geographies and ethnic groups (10, 11). Its annual prevalence in Europe is 1 in 10.000 men and these cases constitute less than 1% of all patients with breast cancer (4). However, this rate is above 6% in Central African countries (12). This relatively higher rate is attributed to liver damage and to endemic

infectious diseases that lead to high levels of estrogen. In Japan, the annual MBC incidence is below five in a million (13). The only race where MBC incidence is above the average is the Jewish men and this characteristic is independent from living in the USA or Israel (14, 15). Based on our current knowledge, there is no convincing evidence that gynecomasty is associated with MBC; however, it is considered that it may be associated with shared hormonal risk factors (10). Breast cancer may be incidentally found in the specimens of cases operated on for gynecomasty, whereas gynecomasty may be found in the specimens of cases operated on for breast cancer (at a rate of 9% to 40%) (16, 17). It is reported that 6% to 38% of patients with breast cancer have clinical gynecomasty. These rates are not different from those of the normal population (18). A positive family history increases the relative risk 2.5 times, and 20% of men with breast cancer have a first degree relative with the same disease (4, 19). While the relative risk for a first second male breast cancers 30 times higher, this rate is only around 2-4 times for women. The risk for breast cancer on the contra lateral side is the highest for those at or below the age of 50, as in women (20, 21).

The known risk factors for male breast cancer are listed in Table 1. The incidence is directly proportional to age. While the age difference between men and women at the time of diagnosis is higher in the USA, this difference is not that high in the Middle East and Southern Asia (22, 23). The risk factor of genetic predisposition in men is similar to that of women. Klinefelter syndrome is the strongest risk factor for MBC and it is seen in approximately one out of every 1000 men (10, 24, 25). Family history of breast cancer brings about a 2.5 times relative risk for men. Nearly 20% of men with breast cancer have a positive family history. BRCA mutations increase the risk for male breast cancer (26). The best-known genetic linkage to MBC is the BRCA2 mutation (27). BRCA1 mutation, however, has a more limited role in MBC. The presence of BRCA2 mutation in sporadic MBC is rare. MBC in patients with the mutation tends to present at a younger age. Similarly, breast cancer in men with Klinefelter Syndrome is detected in the young ages (18). The other genetic factors include androgen receptor (AR) gene, CYP17, PTEN tumor suppressor gene and CHEK2 mutation (28). Nearly 3% to 7.5% of MBC cases have Klinefelter syndrome (28-30). In addition to BRCA1 and BRCA2, CHEK2 is a kinase effective in DNA repair. There is some evidence indicating that CHEK2 creates predisposition to male breast cancer (31).

Several risk factors such as early menarche, late menopause, age at first live birth are still valid for female breast cancer, and are not applicable to men. Several studies evaluating risk factors for male breast cancer have been conducted. The prospective National Institute of Health (NIH)-AARP Diet and Health Study ultimately identified 121 men who developed breast cancer (5). In this analysis, a negative correlation with physical activity was established and having history of a first-degree relative with male breast cancer (relative risk, RR, 1.92; 95%CI 1.24-3.91) and increased body mass index (>30 vs. <25; RR 1.79, 95%CI 1.10-2.91) were found to correlate with increased breast cancer. The factors that influence the ratio of estrogen to androgen, external administration of estrogen or testosterone (32), obesity (29, 33-35), orchitis/epididymitis (29), presence of a history of prostate cancer treated with estrogen (36) and Klinefelter Syndrome (25, 29) increase the risk of male breast cancer. Another study that analyzed the USA Veterans Affairs database detected 642 MBCs (29). The risk factors were found to be the presence of diabetes (RR 1.30, 95%CI 1.05-1.60), orchitis/epididymitis (RR 1.84, 95%CI 1.10-3.08),

**Table 1. Risk factors for male breast cancer (3, 4, 9, 19, 24-29,32-35, 42-47)**

- Age
- Genetic factors
  - Proven
    - Family history
    - BRCA2>BRCA1
  - Potential
    - PALB2
    - Androgen receptor
    - CYP17
    - CHEK2
    - Conditions related to abnormal estrogen-androgen ratio
  - External use of estrogen and testosterone
  - Obesity
  - Orchitis, epididymitis
  - Finasteride
    - Lifestyle
  - Inadequate exercise
    - Exposure
  - Proven
    - Radiation
  - Potential
    - Electromagnetic field
    - Heat
    - Volatile organic compounds (such as tetrachloroethylene, p-chloro-ethylene, trichloroethylene, dichloroethylene, etc.), chemicals
- Other potential risk factors
  - At birth (Potentially a higher risk in first deliveries)
  - Bone fractures after the age of 45

Klinefelter syndrome (RR 29.64, 95%CI 12.26-71.68) and gynecomasty (RR 5.86, 95%CI 3.74-9.17). Interestingly, gallbladder stone was also detected as an important risk factor for Afro-American MBC cases (RR 3.45, 95%CI 1.59-7.47). A very strong association between MBC and Klinefelter was observed in the Veteran study and in several other similar studies. For example, the Swedish Registry study reported a 50-times higher rate of breast cancer in those with Klinefelter Syndrome (25). History of liver disease, past breast and testicular pathologies are other risk factors that have been described (4).

More interestingly, the male breast cancer is stated to be a preliminary finding for other malignant processes. A review focusing on 69 male breast cancer cases identified simultaneous prostate cancer in 12 patients (17% of the cases examined) (37). Actually, there is a theoretical association; the aromatase inhibitor used in MBC treatment increases

serum testosterone levels and enables the growth and proliferation of prostate cancer clones (38). Apart from prostate cancer, there are studies that support the association of MBC with leukemia, pancreas, small intestine and rectum malignancies (39-41). Various epidemiologic studies have been performed (42), professional exposure to certain chemicals such as polycyclic aromatic hydrocarbons (43-45) and electromagnetic field (46, 47) were detected as potential factors in the development of male breast cancer (4, 48, 49).

### Symptoms, Clinical Signs and Manifestations

The most common presentations are painless palpable mass, skin ulceration, and nipple retraction or discharge in approximately 75% of the cases, similar to women (7, 50-53). Since the breast tissue in men is undersized, the nipple is mostly involved at early stages. The incidence of retraction is 9%, discharge 6% and ulceration is 6% (10). The mass is frequently localized to the subareolar region. It is seen less frequently in the upper outer quadrant (54, 55). The left breast is involved more frequently than the right; 1% of the cases are bilateral.

Male patients are frequently at a higher age than female breast cancer (FBC) at diagnosis (5-10 years older) and at a higher stage (27, 56-59).

The staging of the disease during presentation is as follows on the basis of the Tumor-Node-Metastasis (TNM) system presented by the largest case series in the literature: Stage I: 37%, stage II: 21%, stage III: 33%, stage IV: 9% (51, 52, 60, 61). While the period between disease onset and diagnosis was 29 months in the past (62), this period has been reduced to 6 months in the newer series (63). It is evident that the disease is diagnosed at more advanced stages in men as compared to women. In fact, more than 40% of the patients are already at stage 3 or 4 when they present to the clinic. The lesser amount of breast tissue in men also results in the involvement of chest wall at an early stage. For that reason, it has also been stated that the TNM may not be appropriate for men (64).

### Diagnostic Imaging Methods and Differential Diagnosis

The majority of lesions in the male breast are benign and gynecomasty constitutes most of these lesions. Within these, less than 1% is primary breast cancer. Even though male breast is relatively small, mammography (MG) is technically feasible and adds useful information to clinical examination (65). In the presence of a clinically suspicious lesion, MG should be preferred over ultrasonography (USG). Sensitivity and specificity of mammography are reported as 92% and 90%, respectively (66). A normal male breast is essentially composed of fat tissue and contains only a few secretory canals. It does not have Cooper ligaments, and has none or very little ductal and interlobular connective tissue. For that reason, it has a radiolucent appearance on mammography (67). The tumor is visualized on MG as a hyperdense, well defined, lobulated mass with spiculated margins or as a structural distortion. Microcalcification is observed less as compared to FBC; its tendency of clustering is low, and generally appears as wide, round and dispersed calcifications.

Doyle et al. (68) emphasized the radiologic and pathologic differences between male and female breast cancer in their review:

- 1) The incidence of invasive lobular cancer and in-situ disease are lower in men as compared to women.
- 2) Male breast cancer more frequently manifests itself as a locally advanced disease (skin and/or nipple involvement).
- 3) MBCs are more often localized in the subareolar area, whereas FBCs are localized in the upper outer quadrant.

- 4) Malignant calcifications in MBC are less frequent as compared to women.
- 5) Since neoplastic papillary lesions appear as complex cystic lesions and simple cysts are rare in men, cystic lesions should be evaluated in detail.

Invasive cancers typically appear as solid lesions on USG. When suspicious changes are found in USG or MG, further evaluation is required for definitive diagnosis (69, 70). In patients with nipple discharge, an examination with smear may be needed. The extent of the disease should be evaluated via laboratory examination, pulmonary X-ray, bone scintigraphy and dominal computed tomography (CT) (71). Positron emission tomography - computed tomography (PET-CT) is better than PET or computed tomography (CT) alone for assessing the extent of the disease, and especially for accurately identifying small metastases and lymph node metastases as well as the response to chemotherapy (72).

A differential diagnosis should be made between gynecomasty and cancer in masses of the male breast. The most frequent benign mass of the breast, which may be unilateral or bilateral, is gynecomasty (73). It may be generally recognized through physical examination. Gynecomasty is characteristically symmetrical, bilateral and has a discoid shape under the nipple and areola. As for carcinoma, it develops a painless hard mass at an eccentric location. Besides breast cancer, the reasons that cause a mass in the male breast include gynecomasty, abscess, hematoma, lipoma, fat necrosis, ductal ectasia, intraductal papilloma, cyst, and metastatic tumors (74). Metastasis to the breast is generally 5-6 times more often in women as compared to men (approximately 0.5% to 6.6% of breast malignancies), which is accounted for by differences in hormonal and endothelial cell adhesion molecules, as well as in breast size and vascularity (75). The most frequent primary tumors in men, which metastasize to the breast include melanoma, lymphoma, prostate, lung and colon tumors (76).

### Treatment

#### Treatment of early-stage disease

The standard treatment for early stage male breast cancer is surgery followed by adjuvant endocrine treatment, chemotherapy (CT) or radiotherapy (RT) depending on prognostic factors, which is the same as in women.

#### Surgical treatment approach and axillary lymph node dissection

Up until the 1970s, the main surgical method was radical mastectomy as in women. Considering the lesion size, this approach was replaced by less invasive procedures such as modified radical mastectomy over time (77-79). Currently, modified radical mastectomy and axillary lymph dissection or sentinel lymph node biopsy (SLNB) is recommended if the tumor is not fixed to the pectoral muscle (80). Actually, American Society of Clinical Oncology guidelines state that SLNB is appropriate for men (7). Radical mastectomy is performed if there is extensive involvement of the chest wall and Rotter ganglions (78). Breast-conserving surgery (lumpectomy) may be performed in elderly patients, with a serious concomitant disease, who has gynecomasty along with a small tumor since the male breast is small and most tumors have a subareolar location, but this procedure is rarely preferred (81). Adjuvant RT is also added to the treatment of such patients. Surgeries that are more radical do not contribute to survival. In cases with high tumor burden, preoperative CT may be useful. Patients with a metastatic disease or a poor overall condition may receive a combined treatment with simple mastectomy or local tumor excision with postoperative RT (82).

### Radiotherapy (RT)

Radiotherapy is mandatory if breast-conserving surgery is performed (83). However, the data about RT indications following mastectomy are limited. RT is generally applied in case of involvement of the nipple and skin (84). Adjuvant loco-regional RT is performed more often in MBC than in women because of the more advanced stages and the more aggressive progress in males. Post-mastectomy RT decreases local recurrence by 2/3 in women and has a positive effect on long-term survival (85). On the other hand, it is suggested that post-mastectomy RT does not improve local recurrence and survival rates in MBC and that it enables local tumor control but does not influence overall survival (86, 87). However, there is no evidence showing that RT indications need to be different for men than those for women. In summary, RT is recommended in the presence of a positive lymph node, a tumor larger than 5 cm and margin positivity in MBC (71).

### Chemotherapy (CT)

Excluding non-neoplastic reasons, primary and adjuvant chemotherapies have significantly increased the survival rates for 5-10 years (7-9). A limited number of prospective, randomized clinical studies exist, which indicate the benefit of adjuvant systemic therapy for MBC (88). On the other hand, decreased recurrence and mortality rates have been reported with adjuvant CT in retrospective studies (53, 89). Furthermore, the prognosis and response rates to therapy in with metastatic MBC are similar to those of women. For that reason, it is considered that early stage MBC patients would benefit from adjuvant therapy (77). There is not enough information about the poor prognostic factors according to which a decision for adjuvant CT could be taken. Usually, the prognostic factors that are used in women are applied to men. There is an indication for CT in those with positive lymph nodes, in tumors larger than 1 cm, and negative for hormone receptors (90, 55). Triple negativity (hormone receptors and HER2/neu negativity) is a sign of aggressiveness, this suggests a high-risk patient and is accepted as an indication for CT. HER2/neu and p53 expression are indicators for poor prognosis, and these patients may require a more aggressive systemic treatment. For node negative patients, anthracycline-based CT is preferred whereas anthracycline and taxane are used for those with positive lymph nodes. Based on the data from treatments in women, trastuzumab must be administered in case of HER2/neu positivity, in node-positive or high-risk node negative disease (10).

### Adjuvant Endocrine Therapy

Adjuvant endocrine therapy alone or in combination with CT is recommended for MBC patients, based on the positive results in clinical studies on early-stage FBC patients. However, there are only a few retrospective studies on this issue with no randomized clinical trials. These studies also demonstrated decreased recurrence and mortality rates (77, 91). Most male patients are hormone-receptor (HR) positive, and either tamoxifen or another hormone therapy for 5 years is recommended to those with positive estrogen receptor according to their prognostic factors, similar to women (90). There are also studies defending that hormonal therapy should be the primary treatment method since MBC is rich in hormone receptors and is a cancer that is more sensitive to hormones, while other adjuvant therapies need to be administered in large tumors and positive axillary lymph nodes (92). Tamoxifen is the generally accepted medication for hormonal therapy. The role of aromatase inhibitors in adjuvant therapy is limited.

### Treatment of locally advanced disease

The treatment of male patients with T3/T4 or inflammatory breast cancer is initiated with neo-adjuvant CT and surgery is performed on

those whose tumor becomes amenable to operation. Subsequently, adjuvant tamoxifen is recommended for HR positive cases. It should also be kept in mind that adjuvant hormonal therapy may be an alternative to CT in most cases (93).

### Treatment for advanced disease

Approach to metastatic breast cancer is based on the same principles in both men and women. Metastasis is identified at diagnosis in approximately 5-15% of MBC cases. Di Lauro et al. (94) reported that the most frequent location for metastasis visceral in 76% (lung, liver), bones in 20% and soft tissue (skin) in 4% of the cases in their series of 50 male breast cancer cases. For treating metastatic diseases orchiectomy, adrenalectomy and hypophysectomy have been performed in the past. Since the response rate of the more frequent HR-positive tumors to hormone therapy is 25% to 58%, tamoxifen is currently used as first-choice therapy in such tumors. CT is recommended if the tumor is unresponsive to hormonal therapy (95). Progestins, androgens and luteinizing hormone-releasing hormone agonists may be used in hormone therapy, albeit at a lower rate (55). The value of aromatase inhibitors such as anastrozole and letrozole in metastatic breast cancers has not been fully established. Systemic CT is used in male HR-negative patients with a rapidly progressing and life-threatening visceral disease. Although it is thought that trastuzumab may be useful in HER-2/neu positive disease, the data available on this issue is insufficient.

### Pathology

Male breast cancer is different from female breast cancers with respect to clinical-pathologic characteristics. Despite that, the diagnosis and treatment approaches are based on the results obtained in female breast cancers, since the data regarding MBC are mainly composed of retrospective, single-center case series rather than randomized clinical trials (56, 96, 97). Previous studies have demonstrated that the rate of HR positivity in MBC is higher and most patients are more sensitive to anti-hormonal treatment (27). Almost all histologic types pertaining to FBC have also been reported for MBC, with varying rates. According to the SEER data, 93.7% of MBC is ductal or unclassified, and only 1.5% is of the lobular sub-type (96). This rate is in contrast with those in women (12-15%) (54). This is due to the fact that the male breast tissue remains rudimentary. It is generally exposed to increased estrogen concentrations, is not differentiated and does not result in lobular formation. The tumor grade was detected as 12-20% Grade I, 54-58% Grade II and 17-33% Grade III tumors (43). The other histological types are papillary (2.6%) and mucinous (1.8%) tumors (54). MBC shows a higher estrogen and progesterone receptor expression as compared to women (90% ER, 81% PR in males vs. 60-70% ER or PR in females) (96). As for HER-2/neu expression, it is lower in men in comparison to women (55). The molecular subtypes of breast cancer in women have been widely studied in terms of immunohistochemistry and its importance has been proven (98-100). Accordingly, normal breast-like, basal-like, luminal A, luminal B, and HER2-enriched subtypes have been identified. There is no consensus on molecular subtyping of male breast cancer, and the few studies with small group of patients yielded inconsistent results. In a study of 134 cases from multiple centers, Kornegoor et al. observed luminal type A as being the most frequent type with a rate of 75% (101). While luminal type B was the second most frequent type with 21%, the incidence rate of other types was only 4%. Tumors in luminal B subtype tend to have a higher nuclear degree (93). In another study conducted on 960 patients, the patient distribution was as follows: 84.9% HR-positive/HER2-negative, 11.5% HR-negative/HER2-positive, 0.6% HR-positive/HER2-positive and 2.9% Triple negative (102).

### Prognosis, Survival and Prognostic Factors

Despite the decrease in mortality rate in female breast cancers, the mortality rate in MBC remained unchanged since 1975 (103). The most important prognostic indicator is the stage at diagnosis and lymph node involvement (Figure 1). The overall 5-year survival rate is around 40-65% (7, 52, 77, 104). However, when evaluated according to stage at diagnosis; the 5-year survival rate is 75-100% for stage 1, 50-80% for stage 2, and is decreased to 30-60% for stage 3 (52). Although several studies have stated that the prognosis was worse in MBC than in females, it was determined that there were no differences in the prognosis of the two genders when paired according to age and stage (105). A large study with more than 335 male patients found that if nodal status is used to compare MBC and FBC, then the prognosis was similar (106). The less favorable results in male patients are due to the more advanced stage at presentation as well as a higher mean age at presentation leading to more co-morbidity (52, 107). While estrogen-receptor (ER) positive tumors have a better prognosis, no such association has been shown for progesterone (68). HER2 positivity is a poor prognostic characteristic (108). It is reported that survival is shorter and prognosis is poor in basal-like and HER2+/ER- subtypes in comparison to other groups (109). A secondary cancer may develop in 9-12% of MBC cases during follow-up (74, 110). The incidence rate of bilateral breast cancer in men is low (111). In the presence of metastatic disease (bone, lung, liver, brain, etc.), the median survival is reported as 26.5 months (88).

### Conclusion

Breast cancer is a rare disease among men and the number of cases included in studies is small. It may be confounded with benign diseases, and both patients and physicians may underestimate its signs. Since its detection is delayed, the disease is usually at advanced stages at the time

of diagnosis. Breast cancer behaves differently in males. There is a need for multi-center studies with more patients that focus on the treatment, prognosis, tumor biology and parameters influencing survival.

**Author Contributions:** Concept - M.B.; Design - M.Y, A.İ., M.B.; Supervision - A.İ.; Data Collection and/or Processing- M.Y.; Analysis and/or Interpretation - M.Y.; Literature Review - M.Y.; Writing - M.Y.; Critical Review - M.Y., A.İ., M.B.

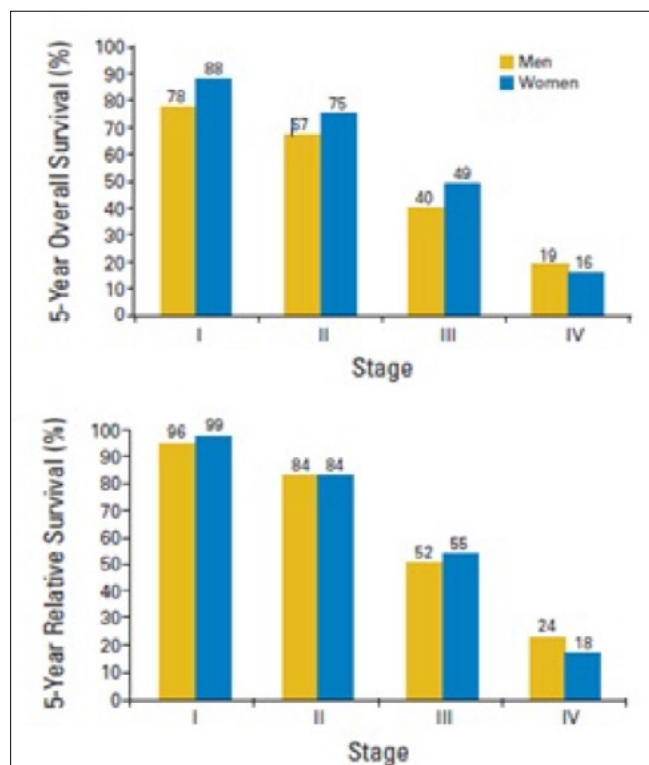
**Peer-review:** Externally peer-reviewed.

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

**Financial Disclosure:** The authors declared that this study has received no financial support.

### References

- Giardano SH. A review of the diagnosis and management of male breast cancer. *Oncologist* 2005; 10:471-479. (PMID: 16079314) [CrossRef]
- Crew KD, Neugut AI, Wang X, Jacobson JS, Grann VR, Raptis G, Hershman DL. Racial disparities in treatment and survival of male breast cancer. *J Clin Oncol* 2007; 25:1089-1098. (PMID: 17369572) [CrossRef]
- National Cancer Institute, Surveillance, Epidemiology, and End Results Program SEER Cancer Statistics Review, 1975-2011. Available from: [http://seer.cancer.gov/csr/1975\\_2011/browse\\_csr.php?sectionSEL=4&pageSEL=sect\\_04\\_table.05.html](http://seer.cancer.gov/csr/1975_2011/browse_csr.php?sectionSEL=4&pageSEL=sect_04_table.05.html).
- Sasco AJ, Lowenfels AB, Pasker-de Jong P. Review article: epidemiology of male breast cancer. A meta-analysis of published case-control studies and discussion of selected aetiological factors. *Int J Cancer* 1993;53: 538-549. (PMID:8436428) [CrossRef]
- Brinton LA, Richesson DA, Gierach GL, Lacey JV, Park Y, Hollenbeck AR, Schatzkin A. Prospective evaluation of risk factors for male breast cancer. *J Natl Cancer Inst* 2008; 100:1477-1481. (PMID: 18840816) [CrossRef]
- International Agency for Research on Cancer. GLOBOCAN 2012. Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Available from: <http://globocan.iarc.fr/pages/online.aspx>
- Cutuli B, Lacroze M, Dilhuydy JM, Velten M, De Lafontan B, Marchal C, Resbeut M, Graic Y, Campana F, Moncho-Bernier V. Male breast cancer: results of the treatments and prognostic factors in 397 cases. *Eur J Cancer* 1995; 31A: 1960-1964. (PMID: 8562148) [CrossRef]
- Cutuli B, Le-Nir CC, Serin D, Kirova Y, Gaci Z, Lemanski C, De Lafontan B, Zoubir M, Maingon P, Mignotte H, de Lara CT, Edeline J, Penault-Llorca F, Romestaing P, Delva C, Comet B, Belkacemi Y. Male breast cancer. Evolution of treatment and prognostic factors. Analysis of 489 cases. *Crit Rev Oncol Hematol* 2010; 73:246-254. (PMID: 19442535) [CrossRef]
- Oger AS, Boukerrou M, Cutuli B, Campion L, Rousseau E, Bussi eres E, Raro P, Classe JM. Male breast cancer: prognostic factors, diagnosis and treatment: a multi-institutional survey of 95 cases. *Gynecol Obstet Fertil* 2015; 43:290-296. (PMID: 25818033) [CrossRef]
- Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. *Lancet* 2006; 367:595-604. (PMID: 16488803). [CrossRef]
- Weiss JR, Moysich KB, Swede H. Epidemiology of male breast cancer. *Cancer Epidemiol Biomarkers Prev* 2005; 14:20-26. (PMID:15668471)
- Surveillance, Epidemiology, and End Results (SEER) Program. Public-use data (1993-1997). Bethesda (MD): National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch; 2000.
- Waterhouse J, Muir C, Correa P, Powell JR, eds. Cancer incidence in five continents, vol 3. IARC Sci Publ 1976; 15.
- Mabuchi K, Bross DS, Kessler II. Risk factors for male breast cancer. *J Natl Cancer Inst* 1985; 74: 371-375. (PMID: 3856050)



**Figure 1.** (A) Overall (B) Relative survival in male and female breast cancer: Surveillance, Epidemiology- and End Results registry, 1973 to 1998 (n=2,537)

15. Steinitz R, Katz L, Ben-Hur M. Male breast cancer in Israel: selected epidemiologic aspects. *J Med Sci* 1981; 17: 816-821. (PMID:7309466)
16. Atalay C, Kanlioz M, Altinok M. Prognostic factors affecting survival in male breast cancer. *J Exp Clin Cancer Res* 2003; 22:29-33. (PMID: 12725319)
17. Koç M, Polat P. Epidemiology and aetiological factors of male breast cancer: a ten years retrospective study in eastern Turkey. *Eur J Cancer Prev* 2001; 10:531-534. (PMID: 11916352) [\[CrossRef\]](#)
18. Wasielewski M, den Bakker MA, van den Ouweland A, Meijer-van Gelder ME, Portengen H, Klijn JG, Meijers-Heijboer H, Foekens JA, Schutte M. CHEK2 1100delC and male breast cancer in the Netherlands. *Breast Cancer Res Treat* 2009; 116:397-400. (PMID: 18759107) [\[CrossRef\]](#)
19. Ewertz M, Holmberg L, Tretli S, Pedersen BV, Kristensen A. Risk factors for male breast cancer - a case-control study from Scandinavia. *Acta Oncol* 2001; 40: 467-471. (PMID: 11504305) [\[CrossRef\]](#)
20. Agrawal A, Ayantunde A, Rampaul R, Robertson JFR. Male breast cancer: a review of clinical management. *Breast Cancer Res Treat* 2007; 103:11-21. (PMID: 17033919) [\[CrossRef\]](#)
21. Auvinen A, Curtis RE, Ron E. Risk of subsequent cancer following breast cancer in men. *J Natl Cancer Inst* 2002; 94:1330-1332. (PMID: 12208898) [\[CrossRef\]](#)
22. Salehi A, Zeraati H, Mohammad K, Mahmoudi M, Talei AR, Ghaderi A, Imanieh MH, Fotouhi A. Survival of male breast cancer in Fars, South of Iran. *Iran Red Crescent Med J* 2011; 13: 99-105. (PMID: 22737442)
23. Tawil AN, Boulous FI, Chakhachiro ZI, Otroock ZK, Kandaharian L, El Saghir NS, Abi Saad GS. Clinicopathologic and immunohistochemical characteristics of male breast cancer: a single center experience. *Breast J* 2012; 18: 65-68. (PMID: 22017630) [\[CrossRef\]](#)
24. Harnden DG, Maclean N, Langlands AO. Carcinoma of the breast and Klinefelter's syndrome. *J Med Genet* 1971; 8:460-461. (PMID: 4337761) [\[CrossRef\]](#)
25. Hultborn R, Hanson C, Kopf I, Verbiené I, Warnhammar E, Weimarck A. Prevalence of Klinefelter's syndrome in male breast cancer patients. *Anticancer Res* 1997; 17:4293-4297. (PMID: 9494523)
26. Martin AM, Weber BL. Genetic and hormonal risk factors in breast cancer. *J Natl Cancer Inst* 2000; 92:1126-1135. (PMID: 10904085) [\[CrossRef\]](#)
27. Giordano SH, Buzdar AU, Hortobagyi GN. Breast cancer in men. *Ann Intern Med* 2002; 137: 678-687. (PMID: 12379069) [\[CrossRef\]](#)
28. Lynch HT, Watson P, Narod SA. The genetic Epidemiology of male breast carcinoma. *Cancer* 1999; 86:744-746. (PMID: 10463967) [\[CrossRef\]](#)
29. Brinton LA, Carreon JD, Gierach GL, McGlynn KA, Gridley G. Etiologic factors for male breast cancer in the US Veterans Affairs medical care system database. *Breast Cancer Res Treat* 2010; 119:185-192. (PMID: 19330525) [\[CrossRef\]](#)
30. Gonzalez KD, Noltner KA, Buzin CH, Gu D, Wen-Fong CY, Nguyen VQ, Han JH, Lowstuter K, Longmate J, Sommer SS, Weitzel JN. Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. *J Clin Oncol* 2009; 27:1250-1256. (PMID: 19204208) [\[CrossRef\]](#)
31. Meijers-Heijboer H, van den Ouweland A, Klijn J, Wasielewski M, de Snoo A, Oldenburg R, Hollestelle A, Houben M, Crepin E, van Veghel-Plandsoen M, Elstrodt F, van Duijn C, Bartels C, Meijers C, Schutte M, McGuffog L, Thompson D, Easton D, Sodha N, Seal S, Barfoot R, Mangion J, Chang-Claude J, Eccles D, Eeles R, Evans DG, Houlston R, Murday V, Narod S, Peretz T, Peto J, Phelan C, Zhang HX, Szabo C, Devilee P, Goldgar D, Futreal PA, Nathanson KL, Weber B, Rahman N, Stratton MR; CHEK2-Breast Cancer Consortium. Low-penetrance susceptibility to breast cancer due to CHEK2 (\*) 1100delC in non-carriers of BRCA1 or BRCA2 mutations. *Nat Genet* 2002; 31:55-59. (PMID: 11967536) [\[CrossRef\]](#)
32. Medras M, Filus A, Jozkow P, Winowski J, Sicinska-Werner T. Breast cancer and long-term hormonal treatment of male hypogonadism. *Breast Cancer Res Treat* 2006; 96:263-265. (PMID: 16418796) [\[CrossRef\]](#)
33. Altinli E, Gorgun E, Karabicak I, Uras C, Unal H, Akcal T. Anthropometric measurements in male breast cancer. *Obesity surgery* 2002; 12:869-870. (PMID: 12568197) [\[CrossRef\]](#)
34. Casagrande JT, Hanisch R, Pike MC, Ross RK, Brown JB, Henderson BE. A case-control study of male breast cancer. *Cancer Res* 1988; 48:1326-1330. (PMID: 3342411)
35. Hsing AW, McLaughlin JK, Cocco P, Co Chien HT, Fraumeni JF Jr. Risk factors for male breast cancer (United States). *Cancer Causes Control* 1998; 93: 269-275. (PMID: 9684707) [\[CrossRef\]](#)
36. Thellenberg C, Malmer B, Tavelin B, Grönberg H. Second primary cancers in men with prostate cancer: an increased risk of male breast cancer. *J Urol* 2003; 169: 1345-1348. (PMID: 12629357) [\[CrossRef\]](#)
37. Lee UJ, Jones JS. Incidence of prostate cancer in male breast cancer patients: a risk factor for prostate cancer screening. *Prostate Cancer Prostatic Dis* 2008; 12:52-56. (PMID: 18504455) [\[CrossRef\]](#)
38. Terris MK, McCallum SW. Re: Aromatase Inhibitors for Male Infertility. *J Urol*. 2002; 168:1509. (PMID: 12352445) [\[CrossRef\]](#)
39. Grenader T, Goldberg A, Shavit L. Second cancers in patients with male breast cancer: a literature review. *Journal of Cancer Survivorship*. 2008; 2:73-78. (PMID: 18648975) [\[CrossRef\]](#)
40. Lowe T, Luu T, Shen J, Bhatia S, Shibata S, Stein A, Somlo G. Male breast cancer 15 years after allogeneic hematopoietic cell transplantation including total body irradiation for recurrent acute lymphoblastic leukemia. *Onkologie*. 2008; 31:266-269. (PMID: 18497517) [\[CrossRef\]](#)
41. Unek IT, Alacacioglu A, Tarhan O, Sevinc AI, Oztop I, Sagol O, Canda T, Obuz F, Balci P, Yilmaz U. Synchronous appearance of male breast cancer and pancreatic cancer 15 years after the diagnosis of testicular cancer-report of a case. *J BUON* 2008; 13:421-424. (PMID: 18979560)
42. Rosenbaum PF, Vena JE, Zielezny MA, Michalek AM. Occupational exposures associated with male breast cancer. *Am J Epidemiol* 1994; 139:30-36. (PMID: 8296772)
43. Hansen J. Elevated risk for male breast cancer after occupational exposure to gasoline and vehicular combustion products. *Am J Ind Med* 2000; 37:349-352. (PMID: 10706746) [\[CrossRef\]](#)
44. Palli D, Masala G, Mariani-Costantini R, Zanna I, Saieva C, Sera F, Decarli A, Ottini L. A gene-environment interaction between occupation and BRCA1/BRCA2 mutations in male breast cancer? *Eur J Cancer* 2004; 40:2474-2479. (PMID: 15519522) [\[CrossRef\]](#)
45. Villeneuve S, Cyr D, Lynge E, Orsi L, Sabroe S, Merletti F, Gorini G, Morales-Suarez-Varela M, Ahrens W, Baumgardt-Elms C, Kaerlev L, Eriksson M, Hardell L, Févotte J, Guénel P et al. Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe. *Occup Environ Med* 2010; 67:837-844. (PMID: 20798010) [\[CrossRef\]](#)
46. Matanoski GM, Breyse PN, Elliott EA. Electromagnetic field exposure and male breast cancer. *Lancet* 1991; 337: 737. (PMID: 1672204) [\[CrossRef\]](#)
47. Tynes T, Andersen A. Electromagnetic fields and male breast cancer. *Lancet* 1990; 336:1596. (PMID: 1979420) [\[CrossRef\]](#)
48. Stenlund C, Floderus B. Occupational exposure to magnetic fields in relation to male breast cancer and testicular cancer: a Swedish case-control study. *Cancer Causes Control* 1997; 8:184-191. (PMID: 9134242) [\[CrossRef\]](#)
49. Cocco P, Figgs L, Dosemeci M, Hayes R, Linet MS, Hsing AW. Case-control study of occupational exposures and male breast cancer. *Occup Environ Med* 1998; 55:599-604. (PMID: 9861181) [\[CrossRef\]](#)
50. Treves N, Holleb AJ. Cancer of the male breast. A report of 136 cases. *Cancer* 1955; 8: 1239-1259. [\[CrossRef\]](#)
51. Scheike O. Male breast cancer. *Acta Pathol Microbiol Scand* 1975:3-35. (PMID: 1138536)
52. Ribeiro GG, Swindell R, Harris M, Baerjee S, Cramer A. A review of the management of the male breast carcinoma based on an analysis of 420 treated cases. *Breast* 1996; 5:141-146. [\[CrossRef\]](#)
53. Stierer M, Rosen H, Weitensfelder W, Hausmaninger H, Teleky B, Jakesz R, Fruhwirth H, Dünser M, Beller S, Haid A. Male breast cancer: Austrian experience. *World J Surg* 1995; 19: 687-693. (PMID: 7571664) [\[CrossRef\]](#)
54. Giordano SH. A review of the diagnosis and management of male breast cancer. *Oncologist* 2005; 10: 471-479. (PMID: 16079314) [\[CrossRef\]](#)

55. Sabel MS. Breast cancer in special populations. In: Sabel MS ed. *Surgical Foundations: Essentials of Breast Surgery*. 1st ed. Philadelphia: Mosby Elsevier; 2009. p. 323-333. [\[CrossRef\]](#)
56. Contractor KB, Kaur K, Rodrigues GS, Kulkarni DM, Singhal H (2008). Male breast cancer: is the scenario changing. *World J Surg Oncol* 16; 6:58. (PMID: 18558006) [\[CrossRef\]](#)
57. Park S, Kim JH, Koo J, Park BW, Lee KS. Clinicopathological characteristics of male breast cancer. *Yonsei Med J* 2008; 49:978-986. (PMID: 19108022) [\[CrossRef\]](#)
58. Anderson WF, Althuis MD, Brinton LA, Devesa SS. Is male breast Cancer similar or different than female breast cancer? *Breast Cancer Res Treat* 2004; 83:77-86. (PMID: 14997057) [\[CrossRef\]](#)
59. Dong C, Hemminki K. Second primary breast cancer following breast cancer in men. *Breast Cancer Res Treat* 2001; 66:171-172. (PMID: 11437104) [\[CrossRef\]](#)
60. van Geel AN, van Slooten EA, Mavrunac M, Hart AAL. A retrospective study of male breast cancer in Holland. *Br J Surg* 1985; 72:724-727. (PMID: 2994794) [\[CrossRef\]](#)
61. Ramantanis G, Besbeas S, Garas JG. Breast cancer in the male: a report of 138 cases. *World J Surg* 1980; 4: 621-624. (PMID: 7233931) [\[CrossRef\]](#)
62. Sachs MD. Carcinoma of the male breast. *Radiology* 1941; 37:458-467. [\[CrossRef\]](#)
63. Wagner JL, Thomas CR, Koh WJ, Rudolph RH. Carcinoma of the male breast: Update 1994. *Med Pediatr Oncol* 1995; 24:123-132. (PMID: 7990761) [\[CrossRef\]](#)
64. Donegan WL, Redlich PN, Lang PJ, Gall MT. Carcinoma of the breast in males. *Cancer* 1998; 83: 498-509. (PMID: 9690543) [\[CrossRef\]](#)
65. Chen L, Chantra PK, Larsen LH, Barton P, Rohitopakarn M, Zhu EQ, Bassett LW. Imaging characteristics of malignant lesions of the male breast. *Radiographics* 2006;26: 993-1006. (PMID: 16844928) [\[CrossRef\]](#)
66. Evans GF, Anthony T, Turnage RH, Schumpert TD, Levy KR, Amirkhan RH, Campbell TJ, Lopez J, Appelbaum AH. The diagnostic accuracy of mammography in the evaluation of male breast disease. *Am J Surg* 2001; 181:96-100. (PMID: 11425067) [\[CrossRef\]](#)
67. Michels LG, Gold RH, Arndt RD. Radiography of gynecomastia and other disorders of the male breast. *Radiology* 1977; 122:117-122. (PMID: 318597) [\[CrossRef\]](#)
68. Doyle S, Steel J, Porter G. Imaging male breast cancer. *Clin Radiol* 2011; 66: 1079-1085. (PMID: 21745659) [\[CrossRef\]](#)
69. Jackson VP, Gilmor RL. Male breast carcinoma and gynecomastia: comparison of mammography with sonography. *Radiology*.1983 Nov;149(2):533 -6. (PMID: 6622700) [\[CrossRef\]](#)
70. Kapdi CC, Parekh NJ. The male breast. *Radiol Clin North Am* 1983; 21:137-148. (PMID: 6836101)
71. NCCN Clinical Practice Guidelines in Oncology. Invasive Breast Cancer (v. 3.2015). Available at: [http://www.nccn.org/professionals/physician\\_gls/pdf/breast\\_basic.pdf](http://www.nccn.org/professionals/physician_gls/pdf/breast_basic.pdf)
72. Yang SK, Cho N, Moon WK. The Role of PET/CT for Evaluating Breast-Cancer. *Korean J Radiol* 2007 8:429-437. (PMID: 17923786) [\[CrossRef\]](#)
73. Gill MS, Kayani N, Khan MN, Hasan SH. Breast diseases in males a morphological review of 150 cases. *J Pak Med Assoc* 2000; 50:177-179. (PMID: 10979622)
74. Eser S. Kanser Kayıtçılığı ve Kanser Kayıt Merkezleri. Ed. Tuncer M. Türkiye'de Kanser Kontrolü. T.C. Sağlık Bakanlığı Kanserle Savaş Dairesi Başkanlığı Yayınları, 2007, 47-77.
75. Burga AM, Fadare O, Lininger RA, Tavassoli FA. Invasive carcinomas of the male breast: a morphologic study of the distribution of histologic subtypes and metastatic patterns in 778 cases. *Virchows Arch* 2006; 449:507-512. (PMID: 17058095) [\[CrossRef\]](#)
76. Macdonald G, Paltiel C, Olivetto IA, Tyldesley S. A comparative analysis of radiotherapy use and patient outcome in males and females with breast cancer. *Ann Oncol* 2005; 16:1442-1448. (PMID: 15972730) [\[CrossRef\]](#)
77. Goss PE, Reid C, Pintilie M, Lim R, Miller N. Male breast carcinoma: a review of 229 patients who presented to the Princess Margaret Hospital during 40 years: 1955-1996. *Cancer* 1999; 85:629-639. (PMID: 10091736) [\[CrossRef\]](#)
78. Borgen PI, Wong GY, Vlamis V, Potter C, Hoffmann B, Kinne DW, Osborne MP, McKinnon WM. Current management of male breast cancer. A review of 104 cases. *Ann Surg* 1992; 215:451-457 [discussion 457-59]. (PMID: 1319699)
79. Heller KS, Rosen PP, Schottenfeld D, Ashikari R, Kinne DW. Male breast cancer: a clinicopathologic study of 97 cases. *Ann Surg* 1978; 188:60-65. (PMID: 208472) [\[CrossRef\]](#)
80. Gough DB, Donohue JH, Evans MM, Pernicone PJ, Wold LE, Naessens JM, O'Brien PC. A 50-year experience of male breast cancer: is outcome changing? *Surg Oncol* 1993; 2:325-333. (PMID: 8130939) [\[CrossRef\]](#)
81. Cutuli B, Dillhuydy JM, De Lafontan B, Berlie J, Lacroze M, Lesanier F, Graic Y, Tortochaux J, Resbeut M, Lesimple T, Gamelin E, Campana F, Reme-Saumont M, Moncho-Bernier V, Cuilliere JC, Marchal C, De Gislain G, N'Guyen TD, Teissier E, Velten M. Ductal carcinoma in situ of the male breast. Analysis of 31 cases. *Eur J Cancer* 1997; 33:35-38. (PMID: 9071896) [\[CrossRef\]](#)
82. Schuchardt U, Seegenschmiedt MH, Kirschner MJ, Renner H, Sauer R. Adjuvant radiotherapy for breast carcinoma in men: a 20-year clinical experience. *Am J Clin Oncol* 1996; 19:330-336. (PMID: 8677899) [\[CrossRef\]](#)
83. Gradishar WJ. Male breast cancer, in Harris JR, Lippman ME, Morrow M, Osborn CK (ed): *Disease of the Breast*. Philadelphia, Lippincott Williams and Wilkins, 2000, pp 661-667.
84. Weiderpass E, Ye W, Adami Ho, Vainio H, Trichopoulos D, Nyren O. Breast cancer risk in male alcoholics in Sweden. *Cancer Causes Control* 2001; 12:661-664. (PMID: 11552714) [\[CrossRef\]](#)
85. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000; 355: 1757-1770. (PMID: 10832826) [\[CrossRef\]](#)
86. Gentilini O, Chagas E, Zurrida S, Intra M, De Cicco C, Gatti G, Silva L, Renne G, Cassano E, Veronesi U. Sentinel lymph node biopsy in male patients with early breast cancer. *The Oncologist* 2007;12: 512-525. (PMID: 17522237) [\[CrossRef\]](#)
87. Gennari R, Curigliano G, Jereczek-Fossa BA, Zurrida S, Renne G, Intra M, Galimberti V, Luini A, Orecchia R, Viale G, Goldhirsch A, Veronesi U. Male breast cancer: a special therapeutic problem. Anything new? (Review). *Int J Oncol* 2004; 24:663-670. (PMID: 14767551) [\[CrossRef\]](#)
88. Bagley CS, Wesley MN, Young RC, Lippman ME. Adjuvant chemotherapy in males with cancer of the breast. *Am J Clin Oncol* 1987; 10:55-60. (PMID: 3825994) [\[CrossRef\]](#)
89. Izquierdo MA, Alonso C, De Andres I, Ojeda B. Male breast cancer. Report of a series of 50 cases. *Acta Oncol* 1994; 33:767-771. (PMID: 7993644) [\[CrossRef\]](#)
90. Jaiyesimi IA, Buzdar AU, Sahin AA, Ross MA. Carcinoma of the male breast. *Ann Intern Med* 1992; 117:771-777. (PMID: 1416579) [\[CrossRef\]](#)
91. Giordano SH, Perkins G, Garcia SM, et al. Male breast cancer: the M.D. Anderson experience with adjuvant therapy. *Breast Cancer Res Treat* 2003; 82: S42.
92. Hayes T. Pharmacotherapy for male breast cancer. *Expert Opin Pharmacother* 2002; 3:701-708. (PMID: 12036409) [\[CrossRef\]](#)
93. Gomez-Raposo C, Zambrana Tevar F, Sereno Moyano M, Lopez Gomez M, Casado E. Male breast cancer. *Cancer Treat Rev* 2010; 36:451-457. (PMID: 20193984) [\[CrossRef\]](#)
94. Di Lauro L, Pizzuti L, Barba M, Sergi D, Sperduti I, Mottolese M, Del Medico P, Belli F, Vici P, De Maria R, Maugeri-Sacca M. Efficacy of chemotherapy in metastatic male breast cancer patients: a retrospective study. *Journal of Experimental and Clinical Cancer Research* 2015; 34:26. (PMID: 25888204) [\[CrossRef\]](#)
95. Yildirim E, Berberoglu U. Male breast cancer: a 22-year experience. *Eur J Surg Oncol* 1998; 24:548-52. (PMID: 9870732) [\[CrossRef\]](#)
96. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN (2004). Breast carcinoma in men: a population-based study. *Cancer* 2004; 101:51-57. (PMID: 15221988) [\[CrossRef\]](#)

97. Anderson WF, Jatoi I, Tse J, Rosenberg PS (2010). Male breast cancer: A population-based comparison with female breast cancer. *J Clin Oncol* 28, 232-9. (PMID: 19996029) [\[CrossRef\]](#)
98. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lønning PE, Børresen-Dale AL, Brown PO, Botstein D. Molecular portraits of human breast tumours. *Nature* 2000; 406:747-752. (PMID: 10963602) [\[CrossRef\]](#)
- 99.. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, Eisen MB, van de Rijn M, Jeffrey SS, Thorsen T, Quist H, Matese JC, Brown PO, Botstein D, Lønning PE, Børresen-Dale AL. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci USA* 2001; 98:10869-10874. (PMID: 11553815) [\[CrossRef\]](#)
100. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, Nielsen TO, Moorman PG, Earp HS, Millikan RC. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA* 2006; 295:2492-2502. (PMID: 16757721) [\[CrossRef\]](#)
101. Kornegoor R, Verschuur-Maes AH, Buerger H, Hogenes Marieke CH, de Bruin PC, Oudejans JJ, van der Groep P, Hinrichs B, van Diest PJ. Molecular subtyping of male breast cancer by immunohistochemistry. *Modern Pathology* 2012; 25:398-404. (PMID: 22056953) [\[CrossRef\]](#)
102. Leone J, Zwenger AO, Iturbe J, Vallejo CT, Leone BA. Prognostic significance of tumor subtypes in male breast cancer: a population-based-study. *Breast Cancer Res Treat* 2015; 152:601-609. (PMID: 26126972) [\[CrossRef\]](#)
103. Nahleh Z. Hormonal therapy for male breast cancer: a different approach for a different disease. *Cancer Treatment Rev* 2006; 32:101-105. (PMID: 16472925) [\[CrossRef\]](#)
104. Joshi MG, Lee AK, Loda M, Camus MG, Pedersen C, Heatley GJ, Hughes KS. Male breast carcinoma: an evaluation of prognostic factors contributing to a poorer outcome. *Cancer* 1996; 77:490-498. (PMID: 8630956) [\[CrossRef\]](#)
105. Willsher PC, Leach IH, Ellis IO, Bourke JB, Blamey RW, Robertson JF. A comparison outcome of male breast cancer with female breast cancer. *Am J Surg* 1997; 173: 185-188. (PMID: 9124623) [\[CrossRef\]](#)
106. Guinee VF, Olsson H, Moller T, Shallenberger RC, van den Blink JW, Peter Z, Durand M, Dische S, Cleton FJ, Zewuster R, et al. The prognosis of breast cancer in males. A report of 335 cases. *Cancer* 1993; 71: 154-161. (PMID: 8416712) [\[CrossRef\]](#)
107. Joshi MG, Lee AK, Loda M, Camus MG, Pedersen C, Heatley GJ, Hughes KS. Male breast carcinoma: an evaluation of prognostic factors contributing to a poorer outcome. *Cancer* 1996; 77: 490-498. (PMID: 8630956) [\[CrossRef\]](#)
108. Rayson D, Erlichman C, Suman VJ, Roche PC, Wold LE, Ingle JN, Donohue JH. Molecular markers in male breast carcinoma. *Cancer* 1998; 83:1947-1955. (PMID: 9806653) [\[CrossRef\]](#)
109. Ge Y, Sneige N, Eltorkey MA, Wang Z, Lin E, Gong Y, Guo M. Immunohistochemical characterization of subtypes of male breast carcinoma. *Breast Cancer Res* 2009; 11:R28. (PMID: 19442295) [\[CrossRef\]](#)
110. Yoney A, Kucuk A, Unsal M. Male breast cancer: a retrospective analysis. *Cancer Radiotherapie* 2009; 13:103-107. (PMID: 19250851) [\[CrossRef\]](#)
111. Goyal A, Horgan K, Kissi M, Yiangou C, Sibbering M, Lansdown M, Newcombe RG, Mansel RE, Chetty U, Ell P, Fallowfield L, Kissin M; AL-MANAC Trialists Group. Sentinel lymph node biopsy in male breast cancer patients. *EJSO* 2004; 30:480-483. (PMID: 15135473) [\[CrossRef\]](#)

# Turkish Ministry of Health, 2<sup>nd</sup> Turkish Medical General Assembly Clinical Oncology Study Group Report

Vahit Özmen<sup>1</sup>, Nergiz Dağoğlu<sup>2</sup>, İsmet Dede<sup>3</sup>, Adem Akçakaya<sup>4</sup>, Mustafa Kerem<sup>5</sup>, Fatih Göksel<sup>6</sup>, Enver Özgür<sup>7</sup>, Emel Başkan<sup>8</sup>, Mustafa Yaylacı<sup>9</sup>, Adil Ceydeli<sup>10</sup>, Meltem Baykara<sup>11</sup>, Huriye Şenay Kızıltan<sup>12</sup>, Şeref Kömürcü<sup>13</sup>, Mahmut Gümüş<sup>14</sup>, H. Mehmet Türk<sup>14</sup>, Recep Demirhan<sup>15</sup>, Ali Akgün<sup>16</sup>, Naim Kadoglou<sup>17</sup>, Emre Yatman<sup>8</sup>, Cem Cüneyt Elbi<sup>18</sup>, Seza Güleç<sup>19</sup>, Atilla Soran<sup>20</sup>, Ahmet Özet<sup>21</sup>, Fahrettin Keleştimur<sup>22</sup>

<sup>1</sup>Department of General Surgery, İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey

<sup>2</sup>Department of Radiation Oncology, İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey

<sup>3</sup>Cancer Surgeon General Office, İstanbul, Turkey

<sup>4</sup>Department of General Surgery, Bezmialem University Faculty of Medicine, İstanbul, Turkey

<sup>5</sup>Department of General Surgery, Gazi University Faculty of Medicine, İstanbul, Turkey

<sup>6</sup>Clinic of General Surgery, Ankara Oncology Training and Research Hospital, Ankara, Turkey

<sup>7</sup>Department of Urology, Köln University Faculty of Medicine, Köln, Germany

<sup>8</sup>Turkey Public Hospitals Institution, Ankara, Turkey

<sup>9</sup>Clinic of Medical Oncology, İstanbul Bayındır Hospital, İstanbul, Turkey

<sup>10</sup>Florida Plastic Surgery Institute, Florida, USA

<sup>11</sup>Clinic of Medical Oncology, Sakarya Training and Research Hospital, Sakarya, Turkey

<sup>12</sup>Department of Radiation Oncology, Bezmialem University Faculty of Medicine, İstanbul, Turkey

<sup>13</sup>Clinic of Medical Oncology, Memorial Hospital, İstanbul, Turkey

<sup>14</sup>Department of Medical Oncology, Bezmialem University Faculty of Medicine, İstanbul, Turkey

<sup>15</sup>Clinic of Thoracic Surgery, Kartal Dr. Lütfü Kırdar Training and Research Hospital, İstanbul, Turkey

<sup>16</sup>Specialty Scanners Ltd, UK

<sup>17</sup>Department of General Surgery, National Health System-Konsultan, Pittsburgh, USA

<sup>18</sup>Bayer Healthcare, USA

<sup>19</sup>Department of General Surgery, Florida International University, Florida, USA

<sup>20</sup>Department of General Surgery, Pittsburgh University Faculty of Medicine, Pittsburgh, USA

<sup>21</sup>National Cancer Institute President

<sup>22</sup>Turkey Health Institute President

## ABSTRACT

**Objective:** There is an increase in the incidence of cancer, and consequently in mortality rates, both in the world and in Turkey. The increase in the incidence and mortality rate of cancer are more prominent in our country as well as in other developing countries. The aim of this workshop was to determine the current status on prevention, screening, early diagnosis and treatment of cancer in our country, to identify related shortcomings, specify solutions and to share these with health system operators, and to aid in implementation of these systems. Developments on palliative care were also evaluated.

**Materials and Methods:** The current situation in the practice of clinical oncology, related drawbacks, problems encountered during multidisciplinary approach and their solutions were discussed under several sub-headings during a 3-day meeting organized by the Turkish Ministry of Health (Türkiye Cumhuriyeti Sağlık Bakanlığı- TCSB) with participation of 16 scientists from Turkey and 6 from abroad, and the conclusions were reported.

**Results:** It is expected that the newly established Turkish Health Institutes Association (Türkiye Sağlık Enstitüleri Başkanlığı-TÜSEB) and the National Cancer Institute (Ulusal Kanser Enstitüsü) will provide a new framework in the field of oncology. The current positive findings include the increase in the number of scientists who carry out successful trials in oncology both in Turkey and abroad, the implementation of the national cancer registry program by the Cancer Control Department and the breast cancer registry program by the Turkish Federation of Breast Diseases Societies (Türkiye Meme Hastalıkları Dernekleri Federasyonu-TMHDF), and introduction of Cancer Early Diagnosis, Screening, and Training Centers (Kanser Erken Tanı, Tarama ve Eğitim Merkezi-KETEM) for the application of community-based cancer screening programs. In addition to these, obvious shortcomings related to education, implementation, management and research issues were also determined, and policy and project proposals to address these issues were presented. Collaboration with relevant organizations in the implementation of these studies was supported.

**Conclusion:** Both the incidence and mortality rates of cancer are increasing in Turkey. The widespread deficiencies in population-based screening and in effective treatment lead to an increase in delay in diagnosis and mortality. Despite improvements in data recording, screening and treatment over the last 10 years, extensive, organized, population-based screening programs and fully equipped early diagnosis and treatment centers are required. Enhancement of basic cancer epidemiologic, translational, genetic and molecular research studies is essential in our country. Improvements on pain treatment and palliative care of patients with chronic and terminal cancer are also required.

**Keywords:** Workshop, cancer, Turkey, incidence, prevention, screening, National Cancer Institute

## Introduction

The incidence and mortality of cancer is increasing all over the world, in parallel to population growth, aging, stress, nuclear waste, obesity, inactivity, improper diet, processed foods, smoking, and alcohol consumption (1-10). In developed countries, lung and prostate cancers are the most common cancer types in men, whereas breast and colorectal cancers are seen more often in women (1, 3, 5). In developing countries, lung, gastric, and liver cancers are common in men, and breast and cervical cancers are seen more often in women (3, 4).

The World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) announced that in 2012, cancer was diagnosed in 14.1 million people and 8.2 million died of cancer worldwide, and that 32.6 million people who were diagnosed as having cancer within the last 5 years are alive (1). Fifty-seven per cent of patients with newly diagnosed cancer (8 million) and 65% of cancer deaths (5.3 million) were reported from developing countries.

The incidence of cancer is 25% higher in men (205/100 000) than in women (165/100 000) (5). The age-adjusted cancer incidence in men in West Africa (79/100 000) is five times less than in Australia (365/100 000), and is three times less in South-Central Asia (103/100 000) than in North America (295/100 000).

The regional differences in mortality are less striking; the mortality rate is 15% higher in men, and 8% higher in women in developed countries than in developing countries (1, 3, 5). The high mortality rate in developed countries is attributed to the significantly higher incidence rate.

The changing lifestyle in Turkey, such as changes in reproductive function, nutritional habits, obesity, inactivity, increased smoking and alcohol use, population growth, aging, and increased awareness have led to an increase in cancer incidence and cancer-related mortality (4). In Turkey, the age-adjusted cancer rates for men and women in 2012 were reported as 277.7/100 000 and 188.2/100 000, respectively (2, 4, 7). The increase in breast cancer incidence could may reflect the increase in cancer incidence in Turkey (9-11). The incidence of breast cancer in Turkey in 1993 was reported as 24/100 000; in the last 20 years it has more than doubled and has reached 50/100 000.

Despite the increase in the incidence of cancer in Turkey, the lack of for nationwide cancer prevention and population-based screening programs, and low cancer awareness remains a significant problem. For these reasons, advanced stages at diagnosis are usual. The rates of stage 0 and I breast cancer are 5% and 27%, respectively, according to the Turkish Federation of Breast Diseases Societies' (Türkiye Meme Hastalıkları Dernekleri Federasyonu-TMHDF) database, which includes more than 22 000 patients (10). There is also a delay in initiating treatment for advanced-stage cancer because of patient and system-related factors (12). In our study, which included 1038 patients with breast cancer, the total delay to treatment initiation was 14.8 weeks, most of which was related with the health system (10.5 weeks) (12).

The increase in cancer incidence and mortality in Turkey has led the Turkish Ministry of Health (TCSB-Türkiye Cumhuriyeti Sağlık Bakanlığı) to establish Cancer Early Diagnosis, Screening, and Training Centers (Kanser Erken Tanı, Tarama ve Eğitim Merkezi-KETEM) in the last 10 years, and aims to expand these centers both in number and distribution within the country, to create and initiate national screening programs, and to re-establish and modernize the already-

existing cancer diagnosis and treatment centers. The facts that 50% of patients with breast cancer within the TMHDF database were aged less than 50 years, and that about half the patients who participated in the Bahçeşehir Community-based Mammography Screening Project and diagnosed with breast cancer were aged 40-49 years, have led the mammography screening age in Turkey to be reduced from 50 years to 40 years (13).

Despite positive developments and breakthroughs in the Turkish health system, and the increase in society's awareness of cancer, neither the number nor the capacity for cancer prevention, screening, early diagnosis centers are sufficient. We know that this situation results in system-related delays in both diagnosis and treatment. Above all, the knowledge level of the target audience on cancer is quite low. Although the government has provided the necessary screening and early detection programs free of charge, the participation rate remains very low.

The aim of this workshop, which was organized by TCSB, was to determine the incidence of cancer in Turkey; stage at diagnosis; our status on prevention, screening, diagnosis, treatment and palliative care; to review basic studies on these issues; to recommend proposals to improve the current status to the level of developed countries; and to share them with health system operators.

## Materials and Methods

The Turkish General Medical Assembly was held in Istanbul from October 29 to 31, 2015, by the Ministry of Health. During the 3-day meetings, the experts were divided into groups on 9 different subjects. One of these groups, the Clinical Oncology Study Group, consisted of 22 invited scientists and experts on cancer; 16 from Turkey, and 6 from the United States, the United Kingdom, and Germany. The fields of expertise of the participants were general surgery, surgical oncology, plastic surgery, urology, radiation oncology, administrative medicine, medical technology, and medical oncology. During the meeting, previously determined topics were discussed, and the final results of discussions and proceedings were shared among the participants (Table 1). The prepared study draft was sent to the participants twice, and they were asked to contribute. This article has been prepared in line with their contributions and criticisms.

## Results

### I. Analysis of the current status in Turkey:

It is expected that the newly-established Turkish Health Institutes Association (Türkiye Sağlık Enstitüleri Başkanlığı-TÜSEB) and the National Cancer Institute (Ulusal Kanser Enstitüsü) will provide a new framework in the field of oncology. The main aims and scopes of the institute should include three main headings: 1) Health Care: Services directed for all people and patients living in Turkey should be addressed under this heading. These services should include healthy living and cancer prevention, rapid and early diagnosis, early and effective treatment, regular follow-up and palliative care. 2) Research: Under this heading, cancer-related demographic, epidemiologic, etiologic, social and cultural background research studies should be performed and enhanced in Turkey. Results from these research studies can demonstrate cancer-related factors, cancer incidence and prevalence by age, frequency, distribution according to regions and cities, and required protective measures and infrastructures. Within the clinical trials; overall cancer incidence, prevalence according to organs, stages, prevention, diagnosis and treatment facilities, and the adequacy of existing infrastructure should be investigated. Basic and clinical

**Table 1. Clinical oncology working group discussion topics**

- 1 The current situation in clinical oncology practice, inadequacies, problems encountered during multidisciplinary practice in our country
- 2 Strategic planning for the future in clinical oncology practice in developed countries
- 3 Medical and pediatric oncology practices and development strategies in our country
- 4 Development strategy for Surgical Oncology in our country and the world
- 5 What tasks should be undertaken by the Cancer Institute to improve clinical oncology
- 6 What should be the future development strategy for Radiation Oncology in our country
- 7 Things to be done for rapid improvement of pre-clinical and clinical research in our country
- 8 Is it necessary to determine the minimum standards of cancer treatment in our country, should the Turkish Cancer Institute take part in such efforts
- 9 What tasks should be undertaken by the Cancer Institute for the development of Clinical Oncology
- 10 Designing palliative care in oncology clinics
- 11 Obstacles in the treatment of chronic pain
- 12 End of life care standards
- 13 Advanced care plan for cancer

cal research centers should be identified, their uniform distribution throughout the nation should be provided, and election of members based on merit and maintenance should be ensured. Basic medical and clinical research projects, “translational” research programs that bridge these two traditional survey areas, relevant research and development (R&D) studies should be performed. 3) Education: Under this heading, platforms for acquisition/generation of knowledge and dissemination of information should be created for physicians, allied health staff, and research scientists working on cancer both within and outside Turkey. These three main goals and service mentality must be in complete harmony in both conceptual and practical application, with clearly defined, written, compulsory job definitions.

The current noted positive findings are the increase in the number of scientists who carry out successful trials in oncology both in Turkey and abroad, the implementation of the national cancer registry program by the Cancer Control Department and the breast cancer registry program by TMHDF; however, the number and application of community-based cancer screening programs and introduction of KETEMs is not sufficient, although these are expected to increase in number.

The noteworthy negative factors were identified as the lack of standardization in medical schools, which are growing in number; lack of their evaluation at regular intervals; lack of standardization and accreditation of cancer screening; early diagnosis and treatment centers; im-

balanced distribution of corporate resources; lack of multidisciplinary studies; lack of communication between the management and system and the scientists-scientific centers; lack of guidelines on screening, diagnosis and treatment appropriate for national socio-cultural and economic structure; not implementing the guideline and programs; lack of audit of cancer diagnosis and treatment centers (e.g. radiology, radiotherapy centers); lack of preclinical and translational research; deficits in the knowledge level of trained scholars in the fields of genetics, molecular oncology and molecular radiobiology; lack of basic research in epidemiology, cancer screening and early diagnosis; lack of research in the field of basic oncology and local oncologic medications; lack of production; absence of palliative care centers; and insufficiency in practices.

## II. Policy Recommendations

Policy recommendations are grouped under four headings; education, application, management, and research. Recommendations are categorized in Table 2.

### A. Education:

The following embodiment is considered to be necessary:

1. Clinical and pre-clinical specialist training programs (Fellowship). These programs should be prepared as institutional programs, under the supervision of universities and academic associations, and within the framework of a standardized curriculum of clinical and laboratory studies.
2. Continuous medical education (CME) and implementation. A standard accreditation system for different formats of meetings, conferences, congresses, workshops (PRA Physician's Recognition Award and Credits System) should be introduced.
3. The establishment of a mechanism and infrastructure for International Education/Teaching
  - 3.1 Invitation of cancer specialists/researchers living abroad to scientific meetings, and planning congress/conferences in collaboration with international institutions/organizations
  - 3.2 Creating links with international institutions/organizations in health care sector based on a mutual exchange of research and education (Organic Affiliation)
  - 3.3 Defining terms of international experience for doctors, health professionals, and researchers who work with cancer, organizing recruitment conditions, and determining the conditions of fund allocation
  - 3.4 Invitations of students, physicians, researchers, experts in a special fields and teachers from developed countries and performing exchange program from Turkey to these countries similar to Erasmus Programs
- 3.5 Establishing Turkish cancer organization/institutions for training and teaching abroad.

Standardization and ensuring quality control have been proposed as being essential for student, resident, and clinical oncology fellowship (surgery, medical oncology, radiation oncology, molecular biology, liaison psychiatry) programs at medical faculties, and teaching and research hospitals. Supporting proficiency tests, the implementation of a CME scoring system, short-term rotation of faculty staff, and implementation of national-international visiting scholars were highlighted to reinforce this suggestion.

Implementation of sub-specialties in oncologic surgery (e.g. breast/endocrine, upper gastrointestinal, colorectal, hepato-pancreato-biliary),

Table 2. Policy suggestions

**A. Education:**

- 1 Standardization of undergraduate, postgraduate and continuing medical education and ensuring regular accreditation  
 Recommendation 1.1: Standardization of medical student, resident and fellowship education in Training and Research Hospitals and Medical Faculties, ensuring quality control  
 Recommendation 1.2: Supporting proficiency tests, implementation of scoring in continuing medical education, short-term rotation of faculty members at national and international institutions as guest lecturers  
 Recommendation 1.3: Establishing sub-specialties particularly in oncological surgery (breast/endocrine, upper gastrointestinal, colorectal, hepato-pancreato-biliary, etc.), providing the relevant fellowship education  
 Recommendation 1.4: Establishing standardized national programs for continuing medical education at medical graduate and fellowship levels  
 Recommendation 1.5: Promotion and accreditation of courses and training programs organized by scientific organizations and associations
- 2 Arranging the distribution of teaching staff  
 Recommendation 2.1: Ensuring distribution of staff according to the priority criteria that will be determined based on the degree of adequacy and comprehensiveness of centers
- 3 Training intermediate personnel  
 Recommendation 3.1: Increasing the number of nurses and technicians specialized in oncology, surgery, radiology/nuclear medicine

**B. Management**

- 1 Increasing the number of cancer early diagnosis and treatment centers according to requirements, accreditation and standardization
- 2 Assessment of the distribution of physicians according to fellowship fields  
 Recommendation 2.1: Ensuring homogenization  
 Recommendation 2.2: Basing manpower calculations on features of the applied treatment instead of the number of patients due to an increase in the time spent per patient parallel to technological developments
- 3 Accreditation of knowledge and skills  
 Recommendation 3.1: Periodic training of healthcare providers at State Hospitals, Universities, Training and Research Hospitals and accreditation of these training  
 Example 3.2: Rewarding knowledge and skills.

**C. Implementation**

- 1 Supporting multidisciplinary approach  
 Recommendation 1.1: Compulsory intra-clinical evaluations such as weekly tumor board meetings, joint review meetings or web-based meetings to facilitate multidisciplinary approach, ensuring their organization and support
2. Supporting palliative care as part of clinical oncology  
 Recommendation 2.1: Aiming training on palliative care for physicians, nurses and health workers  
 Recommendation 2.2: Implementation of the concepts of palliative care and intensive care according to the World Health Organization criteria  
 Recommendation 2.3: Facilitating access to essential medicines for palliative care  
 Recommendation 2.4: Determining the pain scores and the approaches for treatment  
 Recommendation 2.5: Efforts on awareness of both patients and health workers about opioid use  
 Recommendation 2.6: Providing the necessary legal arrangements for advanced cancer care plan (health care proxy, resuscitation support systems, etc.)
- 3 Standardization of Application  
 Recommendation 3.1: Following-up establishment and implementation of national algorithms. The determination of molecular approaches to be used in clinical applications  
 Recommendation 3.2: Regular control of reports guiding diagnosis (pathology, radiology, nuclear medicine) in cooperation with scientific associations, and of diagnostic and treatment centers (radiology, radiotherapy, chemotherapy, surgery, nuclear medicine), and their certification

**D. Research**

- 1 Supporting Preclinical and Clinical Research  
 Recommendation 1.1: Identification of the mandatory requirements (staff, materials, equipment, etc.) in the existing experimental medicine and research institutes and centers, and their correction, modernization and development,  
 Recommendation 1.2: Making facilitative incentives,  
 Recommendation 1.3: The selection of scientists to conduct scientific studies and projects according to scientific merit,  
 Recommendation 1.4: Paying attention to ethical issues in science,  
 Recommendation 1.5: Unbiased evaluation and rewarding of scientists.
- 2 Encouraging collaboration with Turkish academic staff abroad  
 Recommendation 2.1: Opportunities should be created in this area, and be supported by appropriate wage policies.

and training a sufficient number of experts on these subspecialties were emphasized as a necessity.

Supporting courses and training programs organized by scientific organizations and specialist associations, and their inclusion in an accreditation system was proposed by the participants.

It was emphasized that the allocation of staff required to develop and to expand accreditation recommendations should be made based on the adequacy of centers and the degree of sophistication.

The determination of the required number of support staff (e.g. nurses, physicians, assistants, technicians) and generalization of their education as in some advanced health systems will alleviate the burden of doctors and facilitate patients' access for supportive treatment. Palliative Care Nursing Certification Training Program Standards are now in effect (approval number: 816 on 28.09.2015 by TCSB) (2). In-service training courses should be organized for physicians who are responsible for specialist palliative care centers, nurses, and psychologists with this initiative.

## B. Management:

The main administrations (TCSB, TÜSEB, Turkish Cancer Institute, and so on) will determine the number and locations of cancer prevention, early diagnosis, treatment and education centers and hospitals (KETEM, State Hospital, Cancer Diagnosis and Treatment Hospitals, Oncology Institute) through basic studies, provide modern equipment and continuously monitor them. They will provide substantial coordination, and will ensure training of health workers at regular intervals and ensure the training is accredited. In these applications, they will cooperate with professional institutions, associations and universities.

It was stated that due to an increase in the time spent per patient parallel to technological developments, manpower calculations should be based on features of treatment instead of the number of patients.

Organization of a modern cancer registry system, its continuous control, and data sharing all emerge as inevitable necessities to determine a national cancer policy. For this purpose, establishing an adequate secretariat to access the registration program, training, and managing them are also mandatory. Supporting propagation and control of the cancer registry program created by the Cancer Control Department, evaluation of the current data in this program, and sharing these data with the appropriate structures are necessary.

Therefore, the central patient record/data system should be compatible with the electronic file systems, which can be accessed by registered doctors and institutions (consultation notes, imaging, laboratory, and treatment notes), the national health and cancer registration system, and subjective cancer registry systems, and its structure should permit knowledge transfer.

Additionally;

- 1.1 Formatting health records
- 1.2 Standardization of image information system (e.g. PACS, picture archiving and communication system)
  - 1.1.2 A committee/sub-committee for diagnostic-treatment-indications guide: preparation of evidence-based guidelines on specific types of cancer (e.g. NCCN National Comprehensive Cancer Network)

- 1.1.3 Administrative Commission: Interpretation/evaluation of legislative amendments and adaptation in the field of cancer services

- 1.1.3.1 Establishing full-fledged cancer centers (e.g. Comprehensive Cancer Center) approved by The National Cancer Institute, their approval and supervision

- 1.1.4 Ethics Commission: A commission should be established to protect the rights of patients and physicians.

A multidisciplinary approach should form the basis of clinical oncology practice; diagnosis and treatment decisions should be made by a multidisciplinary approach. The organization and support of weekly council meetings, intra-clinical evaluation meetings, and web-based meetings is proposed to facilitate the multidisciplinary approach.

It was emphasized that the new and rapidly developing palliative care in Turkey should be assessed as an integrated component of cancer treatment, which also requires a multidisciplinary approach. To elaborate on this proposal, it was recommended that palliative care training should target physicians, nurses and health officers; concepts of palliative care and intensive care should be organized in accordance with the World Health Organization criteria; access to essential medications should be facilitated; a standardized approach to pain scoring and treatment should be determined; awareness on the use of opioids should be raised in both health workers and patients; and that the necessary legal arrangements should be provided for an advanced-care plan study, including health proxy, and resuscitation support decisions.

Family physicians, at-home healthcare teams, palliative care clinics, and centers that belong to palliative care physicians are accountable for palliative care. Accreditation and standardization of these centers are required. It was suggested that in each province the Ministry of Health should identify a representative to monitor local progress at regular intervals, and report to the main administration.

Considering the developing health tourism in Turkey, indicators in accordance with international standards to show the success of oncologic surgery and post-surgery treatments should be disclosed transparently on a regular basis, and treatment results should be compared with those in developed countries.

It is proposed that national algorithms that aim to ensure the standardization of these practices should be established. The implementation of these algorithms should be monitored and molecular approaches should be configured for clinical applications. It is emphasized that reports that guide diagnosis (pathology, radiology, nuclear medicine) should be standardized in collaboration with scientific organizations.

## C. Research:

Scientific research is the most important value that reflects the development level of a country, not only in the field of oncology, but also in all scientific fields. These studies should be arranged according to needs, especially in basic infrastructure, and must maintain continuity. The studies should be original and must contain common features of their international counterparts. Specific protection of the designers and practitioners of research studies in all aspects and rewarding their efforts will provide an important contribution to the promotion of the emergence of new national and international researchers and who excel in science. This year's award of the Nobel Prize in Chemistry to Prof. Dr. Aziz Sancar, the valuable scientist who carried out his career in the USA after graduating from Istanbul Faculty of Medicine, was a

great pleasure for our country, for the university in the USA in which he works, as well as humanity.

**For scientific research:**

1. Establishing “Translational Research” centers within corporate structures. This type of research is based directly on R & D and covers studies that result in clinical innovation.
2. Creation of prospective clinical research projects within corporate structures. To organize multicenter clinical studies with the participation of universities and academic institutions across the country (as in NSABP, National Surgical Breast and Bowel Project). To create and strengthen cooperation between universities and a culture of research that is unfortunately lacking in our country’s medical tradition.
3. Creation of non-corporate project support mechanisms, programs and infrastructures
  - 3.1 Collaborative projects with TUBITAK
  - 3.2 Creating industry innovative research programs infrastructure (as in Small Business Innovation Research [SBIR] and Small Business Technology Transfer program [STTR])
  - 3.3 Creating infrastructure support for academic research projects. Programs in University structure and Special/Foundation research institute programs
4. Creation of a cancer research database: An electronic database that can be accessed by registered physicians and institutions. Compatible with National health and cancer registration system and centralized patient records/data system, in a structure that can provide knowledge transfer.
5. Forming a biobank

Increasing the limited number of centers in which basic oncology research can be conducted, providing trained scientists and necessary equipment for these centers were deemed to be extremely important for the establishment of our national data and treatment programs. In addition, providing incentives to facilitate scientific projects, selecting scientists to conduct scientific studies and projects according to scientific background and merit, paying attention to ethical rules, and unbiased evaluation and awarding of scientists are also of utmost importance.

Palliative cancer care should be in accordance with current conditions, modern, multidisciplinary, holistic, and based on a patient’s requirements and wishes.

The development of the required palliative care services model for our country through analysis of available cancer data and human resources and to integrate this into the general health system are significant issues.

For the development of this program, it is mandatory to raise awareness about palliative care among health care workers as well as in the community, to disseminate palliative care units throughout the country, and to establish national organization models. Improving multidisciplinary teamwork and training of those within the team, as well as progress in research and quality are also required.

The necessary legal arrangements for such practices should be prepared in our country. These arrangements should include legislation on the establishment of palliative care centers, reimbursement of care services, and regulations on terminal sedation and the right for DNR.

We can classify palliative care barriers in Turkey as follows:

- The low level of awareness of palliative care in the community and health care teams
- Failure of planning palliative care in conjunction with antitumor therapy
- Obstacles in the accessibility of opioids
- Inadequate financial support
- Lack of trained health personnel

Deficiencies in laws relevant to practice.

To improve palliative care, implementation of a national palliative care program, establishment of national palliative care associations, standards relating to symptom control and EOL care, certification programs for doctors and nurses, and reimbursement of home care applications are required. In addition, creation of a pediatric palliative care program, determining the levels of opioids in international narcotics control boards, and increasing the national production capacity of morphine are important.

Thanks to our strong family ties, terminal patient care can be performed effectively at home. However, families should also be trained.

**Project Suggestions**

During the meetings, project proposals to improve cancer prevention, screening, diagnosis, and treatment strategies both in our country and in the world were discussed and configured. These recommendations are divided into two groups: 1. Suggestions for prevention, screening, and registration programs: this involves increasing the number of KETEMs and newly-established prevention, early diagnosis, training and screening centers, their modernization, educating their employees on a regular basis, and their regular control. Similar to the training courses in all cities organized by the Turkish Cancer Control Department together with TMHDF between 2009 and 2011, certification and postgraduate training courses are extremely important examples for the renewal of knowledge and skills of doctors and other health professionals interested in cancer. Such courses should aim at not only training health workers but also the community, and educational films and lectures should be included into primary and secondary school programs. At the same time, it is recommended that screening programs be planned in line with the reality of our country and in accordance with modern scientific developments; community-based screening and early-diagnosis centers should be established similar to the Bahçeşehir Community-based Long-term Mammography Screening Center; the cancer registry system should be elaborated in terms of organ cancers; and that the TMHDF Breast Cancer Registration Program could be used as an example. The cost-effectiveness analysis carried out within this project showed that the Bahçeşehir Screening Project was extremely cost effective, and that patients diagnosed through screening (asymptomatic) were given a chance of living an additional 5.87 years as compared with patients diagnosed without screening (symptomatic) (14).

Today, attention must be paid to individualization of cancer screening and treatment, and to the organization of screening programs based on the characteristics of people who participate in or on the genetic characteristics of detected cancers (15, 16). For this purpose, prospective multicenter clinical trials and genomic/molecular studies should be included within the second group of research projects. The multicenter clinical study designed by TMDFH entitled “Effectiveness of

surgery in patients with metastatic breast cancer” is the first of its kind in the world, which poses a very valuable example in this regard (17). This study investigated whether surgery offers benefit to patients diagnosed as having metastatic disease; the 3-year follow-up results will be published next year. In addition, national and international multicenter studies that evaluated factors that caused delays in breast cancer diagnosis proved that considerable prospective clinical studies could be undertaken in our country (12). Moreover, the İstanbul University Oncology Institute Genetics Center is performing significant studies along with other university genetics and molecular research centers.

#### Activities, Studies, and Co-operations that can be developed

It was emphasized that in order for Turkey to excel in new study fields and important research topics, integrative oncology, genomic profiling, immunotherapy, inflammation, genomics, metabolomics, and nanotechnology issues should be prioritized. Collaboration of universities and scientists who enable progress in these fields without financial sacrifice are important for implementation such studies. The scientific cooperation agreement between Munich Ludwig-Maximilian University and Harvard University for this purpose where their faculty members are trained in Harvard and joint projects are held can be given as an example.

In order to prevent over-diagnosis and treatment in cancer, investigation of the genetic nature of tumors, and individualized diagnosis and treatments become extremely important (15, 16). Thus, unnecessary treatments, complications, and excessive costs related to over-diagnosis and treatment will be avoided. It is emphasized that cost/effectiveness studies on genomic profile evaluations (such as 21-gene profile, Mammaprint, PAM 50, and Endopredict) and specific agreements for their routine use in our country are required (18).

#### Discussion and Conclusion

When viewed globally, it can be determined that cancer incidence and mortality rates have increased, and cancer is the leading cause of mortality (19). These increases are more pronounced in developing countries (20). Therefore, implementation of serious health policies according to the economic, social, and cultural status, and trained health professionals in these countries, and their uncompromising practice are mandatory. Otherwise, serious economic and labor losses will occur due to high morbidity and mortality rates in cancer patients.

In Turkey, there is a serious increase in the incidence and mortality rate from cancer (2, 4, 7, 9). In a study regarding the incidence of breast cancer, the incidence of 24.1/100 000 in 1993 more than doubled to a rate of 50/100 000 in 2010 (10, 11). Changes in lifestyle and reproductive function (Westernizing lifestyle), obesity, increasing awareness of cancer, and the aging population all played an important role in this increase (19).

When developed and developing countries are evaluated separately, it appears that the type and incidence rates of cancers are different. In developed countries, lung and prostate cancers in men, and breast and colorectal cancers in women are more frequent. On the other hand, in developing countries, lung, stomach, and liver cancer in men, and breast and cervical cancers in women are more frequent (3, 19). Therefore, countries need to develop prevention and screening programs based on frequency of the most common cancer.

The first five most common cancer types in our country show similarities to those in the world and other developed countries (1-5, 19). In

Turkey, lung cancer in men (60.4/100 000), and breast cancer in women (46.8/100 000) are the most common cancers (2, 4, 9, 10). Childhood malignant tumors are listed as leukemia, lymphoma, and central nervous system tumors. In young men (aged 15-24 years), testicular cancer and Hodgkin's lymphoma, and in young women, thyroid and Hodgkin's lymphoma are the most common types. The more common types of cancer in developed countries are becoming more common in Turkey, parallel with the aging population and lifestyle changes because cancer is usually a disease associated with advanced age (6).

Based on the frequency of cancer in Turkey and the effectiveness of screening programs, screening programs are being applied for breast, cervical and colorectal cancer in women, and for colorectal cancer in men (2, 4, 7). These screening programs are being implemented in KETEMs founded by the TCSB, Universities, several hospitals, and private associations (13, 20). However, most of these programs are not regular and address-based community screening programs, unlike the Bahçeşehir Mammography Screening Project. Therefore, it is required that this sample screening project should be implemented throughout the country by establishing the infrastructure required for this system and training qualified health workers. In addition, target audiences should have cancer awareness for the implementation of screening programs on a regular basis. Adequate and continuous training programs should be conducted for this purpose (9). This similarity of these programs to programs in developed countries, and maintaining continuity are important.

Lung cancer is the most common type of cancer in men in our country, which is directly related to tobacco use. The law enacted by TCSB prohibiting the use of tobacco products in all indoor areas in 2008 has emerged as a serious step in the prevention of lung cancer in our country (2, 4). Implementing such activities without compromise and identifying the actual reduction in lung cancer incidence due to the prohibition of tobacco use with a regular cancer registry program will have serious deterrent effects and reduce tobacco use (8).

Currently, policies to combat cancer have become an important topic in both national health policies and international quality research studies. In the present context, if the Turkish Cancer Institute, which was established for cancer prevention, early diagnosis and effective treatment, acts for the purposes of its foundation, then one of the most important actions will have been taken in this regard. Similar institutions in countries such as the USA, Canada, France, and Korea have been established much earlier, and in addition to their contribution to cancer control programs in their own countries, they have also contributed to research studies on cancer in the entire world (21). It is one of the most important expectations that this organization prepares the necessary research environment for scientists in our country and abroad, and pioneer original scientific projects. Selection of projects to be implemented and of scientists to participate in these projects should be based on scientific value and merit for achieving reliable outcomes.

Cancer screening, early diagnosis, and effective treatment requires the collaboration of several specialties in medicine (22). The aim of obtaining a successful result can only be achieved by the cooperation of all related medical divisions. As in all areas of health, continuing medical education planning for both before and after graduation, and its implementation, standardization, and accreditation are required for all disciplines within the scope of oncology (23-25). Establishing standards of education and practice at the national level is extremely important for the holistic approach, and a requirement for medical

sciences (26, 27). Organizing weekly tumor councils that require collaboration and controlling such efforts will result in treatment success. For example, an increase in the rates of resection in lung cancer was achieved with the introduction of councils; the unnecessary diagnostic procedures were reduced and treatment delays were avoided (28). The implementation of equipped screening and treatment centers in our country, increasing the number of centers and experts on the subject according to needs, and their homogeneous distribution are essential for success in the early diagnosis and treatment of cancer.

The World Health Organization defines palliative care as an approach aimed at the prevention and relief of suffering by early diagnosis, and thorough evaluation and treatment of pain, physical, psychosocial and spiritual problems in patients facing the life-threatening disease cancer and their relatives (29). In this context, the aims are elimination of pain and other distressing symptoms; offering respect for life and death as a normal process; ensuring elimination of problems with the principle of neither hastening nor postponing death; managing symptoms; and improving quality of life with the active participation of physicians and nurses from specialties such as algology, radiation oncology, medical oncology, psychiatry, physical therapy and rehabilitation, internal medicine, surgical nursing, surgical divisions, and pulmonology (30-33).

In our country, there are very few centers for palliative care of cancer patients and experts on the subject. System operators and educational institutions dealing with this issue should come together, determine the number of patients in need of this approach based on a sound recording program, establish modern centers accordingly, and provide training for employees in these centers.

In conclusion, both the incidence and mortality rates of cancer are increasing in Turkey. The widespread deficiencies in population-based screening and in effective treatment lead to an increase in delay in diagnosis and mortality. Despite improvements in data recording, screening and treatment over the last 10 years, extensive, organized, population-based screening programs and fully equipped early diagnosis and treatment centers are required. Enhancement of basic cancer epidemiologic, translational, genetic and molecular research studies is essential in our country. Improvements on pain treatment and palliative care of patients with chronic and terminal cancer are also required.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - V.Ö., N.D., İ.D., A.A., M.K., F.G., E.Ö., E.B., M.Y., A.C., M.B., H.Ş.K., Ş.K., M.G., H.M.T., R.D., A.A., N.K., E.Y., C.C.E., S.G., A.S., A.Ö., F.K.; Design - V.Ö., N.D., İ.D., A.A., M.K., F.G., E.Ö., E.B., M.Y., A.C., M.B., H.Ş.K., Ş.K., M.G., H.M.T., R.D., A.A., N.K., E.Y., C.C.E., S.G., A.S., A.Ö., F.K.; Supervision - V.Ö.; Funding - V.Ö., N.D., İ.D., A.A., M.K., F.G., E.Ö., E.B., M.Y., A.C., M.B., H.Ş.K., Ş.K., M.G., H.M.T., R.D., A.A., N.K., E.Y., C.C.E., S.G., A.S., A.Ö., F.K.; Materials - V.Ö., N.D., İ.D., A.A., M.K., F.G., E.Ö., E.B., M.Y., A.C., M.B., H.Ş.K., Ş.K., M.G., H.M.T., R.D., A.A., N.K., E.Y., C.C.E., S.G., A.S., A.Ö., F.K.; Data Collection and/or Processing - V.Ö., N.D., İ.D., A.A., M.K., F.G., E.Ö., E.B., M.Y., A.C., M.B., H.Ş.K., Ş.K., M.G., H.M.T., R.D., A.A., N.K., E.Y., C.C.E., S.G., A.S., A.Ö., F.K.; Analysis and/or Interpretation - V.Ö., N.D., İ.D., A.A., M.K., F.G., E.Ö., E.B., M.Y., A.C., M.B., H.Ş.K., Ş.K., M.G., H.M.T., R.D., A.A., N.K., E.Y., C.C.E., S.G., A.S., A.Ö., F.K.; Literature Review - V.Ö., N.D., İ.D., A.A., M.K., F.G., E.Ö., E.B., M.Y., A.C., M.B.,

H.Ş.K., Ş.K., M.G., H.M.T., R.D., A.A., N.K., E.Y., C.C.E., S.G., A.S., A.Ö., F.K.; Writing - V.Ö., N.D., İ.D., A.A., M.K., F.G., E.Ö., E.B., M.Y., A.C., M.B., H.Ş.K., Ş.K., M.G., H.M.T., R.D., A.A., N.K., E.Y., C.C.E., S.G., A.S., A.Ö., F.K.; Critical Review - V.Ö., N.D., İ.D., A.A., M.K., F.G., E.Ö., E.B., M.Y., A.C., M.B., H.Ş.K., Ş.K., M.G., H.M.T., R.D., A.A., N.K., E.Y., C.C.E., S.G., A.S., A.Ö., F.K.; Other - V.Ö., N.D., İ.D., A.A., M.K., F.G., E.Ö., E.B., M.Y., A.C., M.B., H.Ş.K., Ş.K., M.G., H.M.T., R.D., A.A., N.K., E.Y., C.C.E., S.G., A.S., A.Ö., F.K.

**Acknowledgement:** Authors would like to thank Mr. David Chapman for his precious contributions in this manuscript's edition.

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

**Financial Disclosure:** The authors declared that this study has received no financial support

## References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012 CA Cancer J Clin. 2015; 65:87-108. (PMID: 25651787) [CrossRef]
2. T.C. Sağlık Bakanlığı Ulusal Kanseri Kontrol Planı. Available at: [http://www.iccp-portal.org/sites/default/files/plans/Ulusal\\_Kanser\\_Kontrol\\_Planı\\_2013\\_2018.pdf](http://www.iccp-portal.org/sites/default/files/plans/Ulusal_Kanser_Kontrol_Planı_2013_2018.pdf)
3. WHO Global cancer rates could increase by 50% to 15 million by 2020 Available at: <http://www.who.int/mediacentre/news/releases/2003/pr27/en/>
4. T.C. Sağlık Bakanlığı Türkiye Onkoloji Hizmetleri Yeniden Yapılanma Programı Available at: <http://www.rivosem.com.tr/wp-content/uploads/2015/04/T%C3%BCrkiye-Onkoloji-Hizmetleri-Yeniden-Yap%C4%B1land%C4%B1rmaProgram%C4%B1.pdf>
5. [http://globocan.iarc.fr/Pages/fact\\_sheets\\_cancer.aspx](http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx)
6. 58<sup>th</sup> World Health Assembly approved resolution on cancer prevention and control WHA58.22 Geneva: World Health Organization 2005: 2.
7. T.C. Sağlık Bakanlığı Türkiye Kanseri İstatistikleri. Available at: [http://kanseri.gov.tr/Dosya/ca\\_istatistik/ANA\\_rapor\\_2012sooonn.pdf](http://kanseri.gov.tr/Dosya/ca_istatistik/ANA_rapor_2012sooonn.pdf)
8. Anttila A, Pukkala E, Söderman B, Kallio M, Nieminen P, Hakama M. Effect of organized screening on cervical cancer incidence and mortality in Finland, 1963-1995: recent increase in cervical cancer incidence. Int J Cancer 1999; 83:59-65. [CrossRef]
9. Özmen V. Breast cancer in Turkey. Türkiye Klinikleri J Gen Surg-Special Topics 2013; 6:1-6.
10. Özmen V. Breast cancer in Turkey. J Breast Health 2014; 10:98-105. [CrossRef]
11. Fidaner C, Eser SY, Parkin DM. Incidence in Izmir in 1993-1994: first results from Izmir Cancer Registry. Eur J Cancer 2001; 37:83-92. [CrossRef]
12. Özmen V, Boylu S, Ok E, Canturk NZ, Celik V, Kapkac M, Girgin S, Tireli M, İhtiyar E, Demircan O, Baskan MS, Koyuncu A, Tasdelen I, Dumanli E, Özden F, Zaborek P. Factors affecting breast cancer treatment delay in Turkey: a study from Turkish Federation of Breast Diseases Societies. Eur J Public Health 2015; 25:9-14. (PMID: 25096257) [CrossRef]
13. Kayhan A, Gurdal SO, Ozaydin N, Cabioglu N, Ozturk E, Ozcinar B, Aribal E, Ozmen V. Successful first round results of a Turkish breast cancer screening program with mammography in Bahcesehir, Istanbul. Asian Pac J Cancer Prev 2014; 15:1693-1697. (PMID: 24641392) [CrossRef]
14. Ozmen V, Cabioglu N, Gurdal SO, Ozcinar B, Ozaydin N, Kayhan A, Saip P, Aribal E. Bahcesehir Mammography Screening Project (BMSP) is cost effective in a developing Country. SABCS 2015, 7-12 December 2015, San Anonio, Texas, USA.
15. Hamburg MA, Collins FS. The Path to Personalized Medicine. N Engl J Med 2010; 363:301-304. [CrossRef]

16. Longo DL. Tumor Heterogeneity and Personalized Medicine. *N Engl J Med* 2012; 366:956-957. [CrossRef]
17. Soran A, Ozmen V, Ozbas S, Karanlik H, Muslumanoglu M, Igci A, Canturk Z, Utkan Z, Ozaslan C, Evrensel T, Uras C, Aksaz E, Soyder A, Ugurlu U, Col C, Cabioglu N, Bozkurt B, Dagoglu T, Uzunkoy A, Dulger M, Koksall N, Cengiz O, Gulluoglu B, Unal B, Atalay C, Yildirim E, Erdem E, Salimoglu S, Sezer A, Koyuncu A, Gurleyik G, Alagol H, Ulufi N, Berberoglu U, Kennard E, Kelsey S, Lembersky B. Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07-01) Turkish Federation of Societies for Breast Diseases, İstanbul, Turkey. December 10-14, 2013, San Antonio Breast Cancer Symposium 2013, San Antonio, Tx, USA.
18. Ozmen V, Atasoy A, Gokmen E, Ozdogan M, Guler EN, Uras C, Ok E, Demircan O, Isikdogan A, Pilanci KN, Ordu C, Duman O, Ates O, Sen F, Kara H, Oz B, Saip P. Results of the Turkish prospective multi-center study utilizing the 21-gene Oncotype DX assay: Decision impact analysis. 2015 ASCO Annual Meeting *J Clin Oncol* 2015; 33 (suppl; abstr e11515).
19. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mather C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136:5:E359-386. [CrossRef]
20. Ozmen V, Fidaner C, Aksaz E, Bayol U, Dede I, Göker E, Güllüoğlu BM, Işıkdogan A, Topal U, Uhri M, Utkan Z, Zengin N, Tuncer M. Preparation of Early Detection and Screening Programms for breast cancer in Turkey. The report of Early Detection and Screening Committee of The Ministry of Health of Turkey. *J Breast Health* 2009; 5:125-134.
21. Gultekin M. Türkiye Sağlık Enstitüleri Başkanlığı bünyesinde Ulusal Kanseri Enstitüsü ve dünya örnekleri kıyaslaması. Online Sağlık Düşüncesi ve Tıp Kültürü Platformu 2014
22. World Federation for Medical Education Global Standards and Quality Improvement in Basic Medical Education 2012. Available at: <http://wfme.org/standards/bme/78-new-version-2012-quality-improvement-in-basic-medical-education-english/file>
23. World Federation for Medical Education Global Standards and Quality Improvement in Postgraduate Medical Education 2015. Available at: <http://wfme.org/standards/pgme/97-final-2015-revision-of-postgraduate-medical-education-standards/file>
24. World Federation for Medical Education Global Standards and Quality Improvement in Continuing Professional Development of Medical Doctors 2015. Available at: <http://wfme.org/standards/cpd/98-final-2015-revision-of-continuing-professional-development-of-medical-doctors-standards/file>.
25. Dağoglu N, Al-Bahrawy M. Disseminating and Implementing the WFME Report on Standards and Quality Improvement. WFME 2003 World Conference in Medical Education: Global Standards in Medical Education for Better Health Care, 2003, Denmark.
26. Sayek I, Odabasi O, Kiper N. Türk Tabipleri Birliği Mezuniyet Öncesi Tıp Eğitimi Raporu, 2010. Available at: <http://www.ttb.org.tr/kutuphane/mote2010.pdf>
27. Kagan AR. The multidisciplinary clinic. *Int J Rad Oncol Biol Physics* 2005; 61:967-968. [CrossRef]
28. Ruhstaller T, Roe H, Thurlimann B, Nicoll JJ. The multidisciplinary meeting: An indispensable aid to communication between different specialities. *Eur J Cancer* 2006; 42:2459-2462. [CrossRef]
29. World Health Organization. Available at: <http://www.who.int/cancer/palliative/definition/en/>
30. Smith TJ, Temin S, Alesi ER, Abernethy AP, Balboni TA, Basch EM, Ferrell BR, Loscalzo M, Meier DE, Paice JA, Peppercorn JM, Somerfield M, Stovall E, Von Roenn JH. American Society of Clinical Oncology Provisional Clinical Opinion: *J Clin Oncol* 2012; 30:880-887. [CrossRef]
31. Komurcu S. Current status of palliative care in Turkey. *J Pediatr Hematol Oncol* 2011; 33 Suppl 1:S78-80. [CrossRef]
32. Komurcu S, Erkisi M, Bavbek S, et al. Recommendation Rec (2003) 24 of the Committee of Ministers to Member States on the Organisation of Palliative Care. The Council of Europe. Translated into Turkish. İstanbul: Turgut Yayıncılık; 2004.
33. Catane R, Cherny NI, Kloeke M, et al. Handbook of Advanced Cancer Care. Taylor & Francis. London and New York 2006. In: Seref Komurcu, ed. İleri Evre Kanserde Bakım El Kitabı. Ankara: Türkiye Klinikleri; 2009.

# Health Beliefs and Breast Cancer Screening Behavior among a Group of Female Health Professionals in Turkey

Meryem Yılmaz, Tuğba Durmuş

Division of Nurses, Cumhuriyet University Faculty of Medicine, Sivas, Turkey

## ABSTRACT

**Objective:** The purpose of this study was to identify the health beliefs and breast cancer (BC) screening behavior of a group of female health professionals (FHPs) [physicians, nurses and midwives] in Turkey.

**Materials and Methods:** This descriptive study was conducted at primary and secondary level healthcare institutions in Central Anatolia, Turkey. The study group included 720 FHPs. Data was collected by a questionnaire and the Turkish version of Champion's Health Belief Model Scales (CHBMS).

**Results:** The mean age of the FHPs was 30.2 years ( $\pm 6.12$  range; 20-50), 8.9 % of them were  $\geq 40$  years. The majority (93.9%) of FHPs did not have annual mammography (MMG) or clinical breast examination (CBE) (95.1%); and 42.9% reported to perform breast self-examinations (BSE). None of the physicians reported having a CBE or MMG. The physicians' perception of susceptibility, severity and barriers to screening was lower than the nurses and midwives; however, their perception of benefits, self-efficacy and health motivation was higher. The perception of benefit among nurses, and self-efficacy and perception of health motivation among midwives were lower than those of the physicians. The perception of barriers to screening was highest among nurses.

**Conclusion:** The compliance rate with early detection practices for BC screening was low among FHPs. Health beliefs influenced their behavior on BC screening.

**Keywords:** Breast cancer, screening, health behavior, community health workers

## Introduction

Breast cancer (BC) is the most common type of cancer in women in both the world and Turkey, with more than 1.2 million new cases being diagnosed each year (1). BC is a growing problem in developing countries. About half of all BC cases as well as 60% of those leading to death are estimated to occur in economically developing countries (2). The BC mortality rate in developed countries is reported as 30% [190,00 deaths/636,000 cases], while this figure is 43% [221,000 deaths/514,000 cases] in less developed countries (3).

According to the Ministry of Health's cancer statistics data, the incidence of BC in Turkish women was 35.0% in 2005, while this rate raised upto 45.1% by 2011 (4). These figures suggest that the prevention of BC is very important, not only in Turkey, but throughout the world. The primary prevention of BC is complicated. However, BC-related deaths are preventable if the disease is detected at early stages. Early detection of BC can be achieved by following the guidelines on secondary prevention methods; breast self-examination (BSE), clinical breast examination (CBE), and mammography (MMG). Using two or three of these screening methods in combination increases their effectiveness.

Breast cancer -related mortality had been rising in western countries until the mid-1980s. However, this trend has changed and this rate has decreased by over 20% in these countries beginning from 1989, which reflected the importance of early detection, screening MMG and introduction of novel therapies (5).

There is a tendency of diagnosing advanced stage BC in Turkey. The BC-related mortality rate has increased due to lack of organized, comprehensive screening programs. Nonetheless, Turkish health priorities have begun to focus on early detection of BC in recent years. The Ministry of Health Cancer Control Department (2004) developed a national screening program for BC early diagnosis in Turkey (3). However, the implementation of such projects in Turkey is very challenging due to issues related to bureaucracy, authority, co-operation, ignorance etc. Currently, the University Cancer Departments, the National Cancer Advisory Board, and scientific and social organizations

are working collectively to identify and implement a national cancer policy. In this context, the Ministry of Health Cancer Control Department began establishing early cancer diagnosis, screening and education centers (KETEM) in 81 provinces in 2005. The most important goals of KETEM are to create awareness on cancer, to propagate prevention strategies, and to establish face-to-face screening in an effort to contact the Turkish population. The law endorsing these goals was put into action in 2008 and is supported by social institutions that offer early detection methods for BC screening. However, previous studies have clearly shown that BC screening practices are under-used among Turkish women. It was reported that only 27% to 39% of Turkish women performed BSE at least once (6); 23.4% had no knowledge on BC; 27.9% had no concept of BSE; 89.3% never had a MMG; and 75.0% never had a CBE (7). The Turkish Ministry of Health reported that 65.1% of Turkish women never performed BSE, and 80.4% had MMG (2012).

Female health personnel (FHPs) [physicians, nurses and midwives] are expected to play an important role in creating an environment that supports screening behaviors for BC. In countries such as Turkey, they can achieve this goal by acting as positive role models, and by gaining more knowledge on early detection methods (8, 9).

Therefore, it is imperative that FHP comply with BSE, CBE and MMG testing. Previous studies showed that BC screening practices of FHPs was low in Turkey (10-12). Studies from other countries (13, 14) have also reported that engagement of FHPs in screening behaviors was relatively low.

There are limited studies on the beliefs and behaviors of FHPs with regard to BC screening in Turkey (9-12, 15) and in the world (13, 14). In addition to these, the results of several studies carried out in Turkey showed that FHPs may have a low sensitivity with regard to screening behavior. The aim of the present study was to investigate the health beliefs and BC screening behavior in a group of FHPs in our country.

## Materials and Methods

### Study design

The study was conducted as a descriptive survey of FHPs. The study was conducted at a public hospital, a state hospital, and a private hospital in Sivas, Turkey. Nineteen primary health centers were included in the study.

The population of the study included all FHPs who were employed in three hospitals and nineteen primary health centers [physicians (n=125); nurse (n=674); midwives (n=200); total n=1006]. Some FHPs were excluded for reasons such as refusal to participate [nurses (n=87); physicians (n=53); midwives (n=52)], and absence due to illness or maternity [nurses (n=34); physicians (n=34); midwives (n=21)]. Overall, 720 interviews were completed (71.6% response rate). Thirty-eight (5.3%) participants were physicians, 555 (77.1%) were nurses and 127 (17.6%) were midwives. None of the participants was formerly diagnosed with BC, and they were between the ages of 20 and 50 years.

In this study, a questionnaire and Champion's Health Belief Model Scale (CHBMS) were used for data collection.

The questionnaire was composed of three sections: The first section included socio-demographic characteristics such as age, education level, marital status, and profession; the second section included hormonal

features such as age at menarche, number of births, and age at first pregnancy; the third section included factors that affect BC such as presence of benign breast disease, a family history of BC, and attitudes and practices related to BSE, CBE and MMG.

Health beliefs were assessed by using Champion's (1984, 1994) revised CHBMS. This model was developed by Rosenstock and colleagues in 1966, and was revised by Victoria Champion (1993), and has been adapted for BC screening. CHBMS gained international acceptance, and has been used to determine health beliefs related to BC screening behaviors in different populations. The CHBMS incorporates six basic concepts contained in the health belief model; i.e. susceptibility, severity, general health motivation, perceived benefits, barriers, and self-efficacy in oneself as they relate to BC, BSE, and MMG (16). All items from the subscales were scored by a five-point scale. Each individual received six separate scores. In this study, the Turkish version of CHBMS translated by Karayurt and Dramalı was used (17). The reliability coefficient for the Turkish version of CHBMS was calculated using Cronbach's alpha, and it ranged from 0.58 to 0.89 for each subscale.

Data was simultaneously collected at each study site between March 16 and April 17, 2010. The purpose of the study was explained to the FHPs who had agreed to participate. The researchers filled out the data collection forms during face-to-face interviews with the FHPs. The researchers interviewed each FHP in their own room. Each interview continued for approximately 20-25 minutes.

### Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences 14.0 (SPSS Inc.; Chicago, IL, USA). Descriptive statistics were used to evaluate the socio-demographic characteristics and early detection practices (BSE, CBE and mammography). The median, mean, and standard deviation (SD) were calculated for HBM scores. Variance analyses (ANOVA) were used for comparisons of HBM scores among groups. Statistical significance was set at 0.05.

## Results

Demographic data were presented in detail in Table 1. Seven hundred twenty (71.57%) FHPs participated in the study. Thirty-eight (5.3%) of the participants were physicians, 555 (77.1%) were nurses, and 127 (17.6%) were midwives. The participant's  $M_{age} = 30.22$  years, with an age range of 20-50 years. The majority of the respondents (656; 91.1%) were younger than 40 years of age. Most of them (448; 62.2%) were married. The nurses were younger than the midwives and physicians. 43.5% of the total study subjects, 43.4% of the nurses, 41.7% of the midwives, and 50% of the physicians had a bachelor's degree. The onset of menarche in 98.1% of the women was  $\geq 12$  years of age, the age at menarche was  $M_{age} = 13.42$  years. The mean age at first pregnancy was higher in physicians as compared to the other two occupational groups, and there was no family history of BC or benign breast disease reported among physicians.

Table 2 displays the rate of FHPs who complied with BC screening methods. As shown in the table, 42.9% of the FHPs reported that they performed BSE, 4.9% underwent CBE and 6.1% had a MMG. None of the physicians reported having a CBE or MMG.

A comparison of participants' average scores for the CHBMS sub-scales were presented in Table 3. The physicians' sensitivity and perception of severity and barriers to screening were lower than those observed in the nurses and midwives; however, their perceptions of benefits, self-

Table 1. Participant characteristics

| Variables*                                | Nurse<br>(n=555) |        | Midwife<br>(n=127) |        | Physician<br>(n=38) |        | Total<br>(n=720) |        |
|-------------------------------------------|------------------|--------|--------------------|--------|---------------------|--------|------------------|--------|
|                                           | n                | %      | n                  | %      | n                   | %      | n                | %      |
| Age (years)                               |                  |        |                    |        |                     |        |                  |        |
| <40                                       | 510              | 91.9   | 110                | 86.6   | 36                  | 94.7   | 656              | 91.1   |
| ≥40                                       | 45               | 8.1    | 17                 | 13.4   | 2                   | 5.4    | 64               | 8.9    |
| Age, years [mean ± SD]                    | 29.7             | (6.01) | 31.6               | (6.30) | 31.7                | (6.01) | 30.2             | (6.12) |
| Education degree                          |                  |        |                    |        |                     |        |                  |        |
| Nursing school graduate                   | 108              | 19.5   | 66                 | 52.0   | 0                   | 0      | 174              | 24.2   |
| Associate degree                          | 186              | 33.5   | 8                  | 6.3    | 0                   | 0      | 194              | 26.9   |
| Undergraduate degree                      | 241              | 43.4   | 53                 | 41.7   | 19                  | 50.0   | 313              | 43.5   |
| Master's and doctoral graduates           | 20               | 3.6    | 0                  | 0      | 19                  | 50.0   | 39               | 5.4    |
| Age at menarche (years)                   |                  |        |                    |        |                     |        |                  |        |
| <12                                       | 10               | 1.8    | 2                  | 1.6    | 2                   | 5.3    | 14               | 1.9    |
| ≥12                                       | 545              | 98.2   | 125                | 98.4   | 36                  | 94.7   | 706              | 98.1   |
| Age at menarche, years [mean±SD]          | 13.37            | (1.17) | 13.52              | (1.35) | 13.71               | (1.21) | 13.42            | (1.21) |
| Parity                                    |                  |        |                    |        |                     |        |                  |        |
| Parous                                    | 277              | 49.9   | 84                 | 66.1   | 27                  | 71.1   | 388              | 53.9   |
| Nulliparous                               | 278              | 50.1   | 43                 | 33.9   | 11                  | 28.9   | 332              | 46.1   |
| Age at first pregnancy, years [mean ± SD] | 24.5             | (1.73) | 22.7               | (2.41) | 27.0                | (0.92) | 24.3             | (2.13) |
| Family history of BC                      |                  |        |                    |        |                     |        |                  |        |
| Yes                                       | 12               | 2.2    | 2                  | 1.6    | 0                   | 0      | 14               | 1.9    |
| No                                        | 543              | 97.8   | 125                | 98.4   | 0                   | 0      | 706              | 98.1   |
| Benign breast disease                     |                  |        |                    |        |                     |        |                  |        |
| Yes                                       | 7                | 1.3    | 1                  | 0.8    | 0                   | 0      | 8                | 1.1    |
| No                                        | 548              | 98.7   | 126                | 99.2   | 0                   | 0      | 712              | 98.9   |

\*All associations were statistically significant at  $p<0.000$

SD: standard deviation; BC: breast cancer

efficacy and health motivation were higher. The perception of benefit among nurses, as well as self-efficacy and perception of health motivation among midwives were lower than those of the physicians. The perception of barriers to screening was higher among nurses. The difference among groups was statistically significant ( $p=0.001$ ).

Table 4 demonstrates BC screening behaviors according to age group, and presence of family history or benign breast disease in FHPs. Among FHPs who were 40 years or older, only 5 (0.7%) had MMG and 2 (3.1%) had CBE. MMG rate was also low among FHPs with a family history of BC and benign breast disease.

Table 5 presents the correlation of CHBMS subscales with BSE, CBE and MMG performance rates among FHPs. The FHPs who performed BSE had low sub-scale scores on perceived susceptibility, severity, perceived barriers along with a high score on self-efficacy. The only significant difference was detected between those who performed BSE and those who did not in terms of all CHBMS sub-scales. The FHPs with MMG had higher perceived susceptibility and severity scores,

and those without any MMG had a high self-efficacy score. There was a significant difference between these two groups in perceived susceptibility sub-scale scores. The FHPs who had a CBE showed higher susceptibility, severity, perceived barriers and health motivation scores on CHBMS than those who did not have a CBE; however, the differences were not statistically significant.

## Discussion and Conclusions

The present study showed that compliance with BC screening methods was extremely low among FHPs. Reports from similar studies on FHPs in Turkey (10, 11, 15, 18) and other countries (13, 14, 19-21) are consistent with the results of this study. As is already known, FHPs are given theoretical information about BC and screening behaviors as part of their training. Prior studies suggested that knowledge leads to improved attitudes and practice due to increased awareness (20, 22). However, information is not always sufficient to increase compliance. The transformation from information to behavior depends on social influences as well as personal emotions such as sensitivity and belief in

Table 2. BC Screening behaviors among FHPs (n=720)

| Screening behaviors | Profession             |                          |                           |                        |
|---------------------|------------------------|--------------------------|---------------------------|------------------------|
|                     | Nurse (n=555)<br>n (%) | Midwife (n=127)<br>n (%) | Physician (n=38)<br>n (%) | Total (n=720)<br>n (%) |
| Performing BSE      |                        |                          |                           |                        |
| Yes                 | 223 (40.2)             | 62 (48.8)                | 24 (63.2)                 | 309 (42.9)             |
| No                  | 332 (59.8)             | 65 (51.2)                | 14 (36.8)                 | 411 (57.1)             |
| Having a CBE        |                        |                          |                           |                        |
| Yes                 | 29 (5.2)               | 6 (4.7)                  | 0                         | 35 (4.9)               |
| No                  | 526 (94.8)             | 121 (95.3)               | 38 (100.0)                | 685 (95.1)             |
| Having a mammogram  |                        |                          |                           |                        |
| Yes                 | 33 (6.0)               | 11 (8.7)                 | 0                         | 44 (6.1)               |
| No                  | 522 (94.0)             | 116 (91.3)               | 38 (100.0)                | 676 (93.9)             |

BC: breast cancer; FHPs: female health professionals; BSE: breast self-examination; CBE: clinical breast examination

Table 3. Comparison of health beliefs among FHPs

| CHBM sub-scales          | Nurse (n=555)<br>Mean ± SD | Midwife (n=127)<br>Mean ± SD | Physician (n=38)<br>Mean ± SD | F      | p     |
|--------------------------|----------------------------|------------------------------|-------------------------------|--------|-------|
| Perceived Susceptibility | 5.28±1.98                  | 5.73±2.16                    | 4.08±1.42                     | 10.176 | 0.001 |
| Perceived severity       | 21.83±5.09                 | 21.15±5.70                   | 15.94±4.75                    | 23.142 | 0.001 |
| Perceived benefits       | 16.04±2.93                 | 16.24±2.45                   | 17.08±2.95                    | 2.475  | 0.085 |
| Perceived barriers       | 21.33±6.95                 | 19.32±6.16                   | 14.08±4.50                    | 23.579 | 0.001 |
| Self-efficacy            | 42.43±5.21                 | 41.65±5.42                   | 46.37±4.74                    | 12.103 | 0.001 |
| Health motivation        | 27.23±3.99                 | 25.78±3.88                   | 31.79±3.73                    | 33.609 | 0.001 |

FHPs: Female Health Professionals; CHBM: Champion's Health Belief Model; SD: standard deviation

Table 4. Screening behaviors according to age group and presence of family history and benign breast disease among FHPs

| Screening behaviors | ≤40 yr<br>(n=656)<br>n (%) | ≥40 yr<br>(n=64)<br>n (%) | Family history*<br>(n=14)<br>n (%) | Benign breast disease*<br>(n=8)<br>n (%) |
|---------------------|----------------------------|---------------------------|------------------------------------|------------------------------------------|
| Performing BSE      | 276 (42.1)                 | 33 (51.6)                 | 4 (36.5)                           | 6 (75.0)                                 |
| Having a CBE        | 33 (5.0)                   | 2 (3.1)                   | 6 (42.9)                           | 6 (75.0)                                 |
| Having a MMG        | 39 (5.9)                   | 5 (7.8)                   | 5 (35.7)                           | 3 (37.5)                                 |

\*There are multiple answers  
BSE: breast self-examinations; CBE: clinical breast examination; MMG: mammography; FHPs: female health professionals

preventive behaviors. Cultural and psychosocial factors are also important for behavior change (23). In addition to information, protective health behaviors such as screening are related to perceptions of risk, benefit and barriers associated with personal and social attitudes and influences. Champion (24) stressed that health beliefs play an important role in an individual's interest in protective health behaviors that lead to action. Karayurt and Dramalı (17) reported that BC screening behavior was associated with health beliefs among Turkish women. In

the current study, most of the FHPs were relatively young, did not have a history of benign breast problems or a family history of BC. Based on their scores on perception of risk and benefits of screening, it may be concluded that they do not perceive themselves as an at-risk group. This factor might have caused the low scores regarding BC screening behavior. Nevertheless, the presence of risk factors is not diagnostic per se, i.e. most women with one or more BC risk factors never develop the disease while many women without any apparent risk factor have

Table 5. Correlation of health beliefs and BC screening behaviors among FHPs

|                        | Screening behaviors |             |            | CHBM sub-scales |               |                   |
|------------------------|---------------------|-------------|------------|-----------------|---------------|-------------------|
|                        | Susceptibility      | Severity    | Benefits   | Barriers        | Self-efficacy | Health Motivation |
| <b>BSE performance</b> |                     |             |            |                 |               |                   |
| Yes (n=309)            | 4.96±1.95           | 20.64 ±5.68 | 16.86±3.33 | 16.01±5.26      | 45.13±4.90    | 28.09±4.88        |
| No (n=411)             | 5.55±2.03           | 21.97±5.00  | 15.59±2.32 | 23.99±5.98      | 40.56±4.73    | 27.17±4.10        |
| t                      | -3.895              | -3.331      | 6.037      | -18.631         | 12.617        | 11.194            |
| p                      | 0.001               | 0.001       | 0.001      | 0.001           | 0.001         | 0.001             |
| <b>CBE performance</b> |                     |             |            |                 |               |                   |
| Yes (n=35)             | 8.00±3.31           | 22.20±6.36  | 15.11±3.80 | 23.06±7.03      | 41.41±5.03    | 28.1±4.9          |
| No (n=685)             | 5.17±1.83           | 21.37±5.29  | 16.18±2.80 | 20.47±6.89      | 42.56±5.32    | 27.2±4.1          |
| t                      | 8.384               | 0.895       | -2.119     | 2.133           | -1.231        | 1.256             |
| p                      | 0.001               | 0.371       | 0.034      | 0.033           | 0.219         | 0.210             |
| <b>Mammography</b>     |                     |             |            |                 |               |                   |
| Yes (n=44)             | 7.64±2.64           | 22.18±3.93  | 15.18±1.77 | 24.57±6.07      | 38.52±3.61    | 26.61±4.46        |
| No (n=676)             | 5.15±1.87           | 21.36±5.42  | 16.19±2.91 | 20.33±6.90      | 42.77±5.3     | 27.26±4.12        |
| t                      | 8.307               | 0.995       | -2.275     | 3.972           | 5.23          | -0.999            |
| p                      | 0.001               | 0.320       | 0.023      | 0.001           | 0.001         | 0.318             |

BSE: breast self-examinations; CBE: clinical breast examination; FHPs: female health professionals; BC: breast cancer; CHBMS: Champion's Health Belief Model Scales

BC. The 10-year follow-up data from randomized controlled trials showed a modest benefit of screening in the younger age groups (25). Nevertheless, it was reported that 75% of patients who were diagnosed with stage I disease at KETEM were under 50 years of age (26).

The “guarding against cancer” theory describes and explains the conditions, actions, and consequences involved when a woman 55 years of age or older, with a family history of BC makes decisions about whether or not to undergo screening MMG. The process of guarding against cancer is usually the result of a triggering event that causes participants to become aware of their BC risk. These events include having a friend or family member diagnosed with BC, and discovering a breast change by themselves or their healthcare provider. Risk awareness often leads to BC screening. The actions that women take in guarding against cancer include taking charge of their health status and keeping faith. Therefore, women with a first-degree relative with BC reacts by having a MMG, getting health check-ups, developing healthy behaviors, and being optimistic (27).

Our study revealed that the rate of obtaining MMG and CBE was low among nurses and midwives. None of the physicians reported having a CBE or MMG. In concordance with our study, Ibrahim and Odusanya (14) reported a low rate of obtaining CBE and MMG in the majority of FHPs. Uncu and Bilgin (28) determined rates of BSE performance as 56.1%, CBE as 40.3%, and MMG as only 25.4% among nurses and midwives. Al-Naggar and colleagues (29) reported that only 25.7% of physicians underwent screening MMG. In a study by Akpınar et al. (12), the rate of having a MMG was reported as 10.1% and the rate of CBE as 24.8%. The low rates of obtaining CBE and MMG may be related to the fact that these procedures require hospital visits, specialized equipment, expertise and cost.

Both diagnostic and screening MMG are funded by national health insurance and are free of charge in Turkey. However, studies have shown that BC screening practices are underused among Turkish women, of whom 89.3% never had a MMG, and 75.0% never had a CBE (7). In a previous Turkish study (30), it was found that having a CBE was strongly associated with the use of MMG. In the literature, undergoing regular CBE and MMG have been associated with the concepts of HBM including perceived susceptibility and severity of BC, benefits and barriers to CBE and MMG, and health motivation (24, 31).

The current study indicated that self-efficacy had the lowest score in health beliefs among midwives. Self-efficacy is associated with increased confidence in executing a behavior and with an increase in compliance with a given behavior (31). Health motivation, perceived benefits and self-efficacy had the highest scores whereas perceived barriers had the lowest score in health beliefs among physicians. A previous Turkish study (10) found that physicians' health motivation and self-efficacy scores were higher than those of the nurses and midwives. In another similar study (21), it was found that the physicians' health motivation, self-efficacy, perceived benefits scores were higher than those of the nurses, midwives and other participants. According to the HBM, the rate of compliance with regular screening methods is higher in women with higher scores of health motivation and self-efficacy. The concept of self-efficacy is based on Bandura's (32) social cognitive theory. It refers to the belief that one can successfully execute a particular behavior in order to achieve a given outcome. The concept of self-efficacy is associated with perceived behavioral control. According to Bandura, expectations such as motivation, performance, and feelings of frustration associated with repeated failures determine affect and behavioral reactions (33). The high rate of BSE performance among physicians was thought to be associated with high self-efficacy and health motiva-

tion along with low perceived barriers. Perceived barrier is a significant factor influencing BC screening behavior. Perceived barriers refer to the perceived disadvantages of adopting a recommended action as well as perceived obstacles that may prevent or delay its successful performance. Thus, lower perceived barriers are assumed to lead to a high probability of adopting the recommended screening behaviors (31). It is reported that lack of confidence was the most frequent barrier to adopting early-detection methods (34).

In the present study, scores of perceived susceptibility, severity and perceived barriers were low among those who performed BSE. There was a statistically significant difference between those who performed BSE and those who did not in all sub-scale scores of CHBMS. High susceptibility and severity scores along with low perceived barriers are commonly assumed to combine additively to influence the likelihood of performing a behavior (33).

Our results revealed that perceived barriers and susceptibility were higher in FHPs who had a CBE and MMG. This result indicates that BC is sensitive to. However, the high perception of barriers may be due to barriers such as physical discomfort or inconvenience, fear of radiation and fear of detection of cancer that were significant predictors associated with whether or not women would obtain a MMG. Another study (35) reported that FHP's awareness on MMG as a diagnostic method was very high (80.7%); however, the actual rate of obtaining MMG was only 3.1%. Recently, in the study of Shiryazdi (21) [2014], it was found that only 10.6% of the study population underwent MMG, and that perceived barriers were low among those who had performed BSE and MMG.

The social psychological model suggests that behavior is determined by the intention to perform a behavior. This intention, in general, is determined by three important factors: Attitudes, social influences, and self-efficacy (36). Any given behavior reflects the attitudes and innate emotions of an individual. Behavior is also influenced by the belief that a certain action will benefit the individual. With regard to health related beliefs, the associated behaviors imply an individual's interest in actions that are potentially protective (31). Perceived susceptibility, perceived benefits of and perceived barriers to the action are central components of the HBM. Perceived benefits refer to the perception of positive outcomes thought to result from a behavior, while perceived barriers pertain to negative attributes related to the health action. Clarification of the relationships between susceptibility, benefits, barriers and compliance with MMG recommendations is critical in determining their influence on screening behavior (24).

In addition to these, studies have shown that physicians can play a significant role in motivating women to participate in initial and subsequent BC screening (37). It was reported (22) that there was an improvement in physicians' attitudes and practice after an educational program on BC, which suggests that continued and repeated educational courses are necessary for improved compliance with BC screening. It is well known that physicians, nurses and midwives are a direct source of health information for patients.

Female health professionals' personal perceptions of their own BC risk and the benefits of screening may influence whether they recommend BC screening to their patients or not. Moreover, providers who do not themselves adhere to screening guidelines may be less likely to promote these behaviors among patients and are likely to be less effective when they do make such recommendations.

The results of this study suggested that the compliance rate with early detection practices for BC screening were low among FHPs, and that health beliefs influenced their behavior on BC screening. These findings provide important information on the level of BC awareness and practice among FHPs. Change in the attitudes and behaviors of FHPs with regard to BC screening would likely influence the information provided for their patients and their BC screening behavior. Therefore, targeted interventions should be developed to improve awareness in FHPs. Undergraduate and continuing education programs are required to achieve improvements in BC screening behavior.

The use of MMG, a breast imaging technique, is the most common secondary preventive method that can detect BC undetectable by BSE at an early stage. MMG has been widely used for screening of asymptomatic women over 40 years of age, for diagnostic purposes, and for monitoring high-risk individuals since it decreases BC-related mortality. However in this study, the rate of applying BC screening methods was lower in FHPs who were accepted as high-risk individuals; those over 40 years of age, with a familial history of BC and benign breast disease (Table 4). Results of this study indicate that the compliance rate with early detection practices for BC screening was low among FHPs, and that their health beliefs influenced their behavior towards BC screening.

**Ethics Committee Approval:** An ethical committee on non-invasive clinical research was not in action in Cumhuriyet University during the study period. Written consents were obtained from all participating institutions. All procedures adhered to the ethical principles of the Helsinki Declaration. FHPs were invited to participate in the study and were informed on all aspects of the study.

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

**Author Contributions:** Concept - M.Y., T.D.; Design - M.Y., T.D.; Supervision - M.Y.; Data Collection and/or Processing - T.D.; Analysis and/ or Interpretation - M.Y.; Literature Review - M.Y.; T.D.; Writer - M.Y.; Critical Review - M.Y.

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

**Financial Disclosure:** The authors declared that this study has received no financial support.

## References

1. WHO Cancer, Fact Sheet 297. World Health Organization Media Centre, Geneva 2011; Retrieved from <http://www.who.int/mediacentre/factsheets/fs297/es/index.html> on 02 May 2014.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global Cancer Statistics. *CA Cancer J Clin* 2011; 61: 69-90. (PMID: 21296855) [CrossRef]
3. Özmen V, Fidaner C, Aksaz E, Bayol Ü, Dede I, Göker E, Göker E, Güllüoğlu BM, Isıkdoğan A, Topal U, Uhri M, Utkan Z, Zengin N, Tuncer M. Organizing early diagnosis and screening programs for breast cancer in Turkey "The report of Breast Cancer Early Detection and Screening Sub-Committee, National Cancer Advisory Board, The Ministry of Health of Turkey". *J Breast Health* 2009; 5: 125-134.
4. The Republic of Turkish Ministry of Health. Organs, gender and age distribution of cancer incidence and the 10 most common cancers in women. *Cancer Center* 2012; Available from <http://sbu.saglik.gov.tr/Ekutuphane/kitaplar/istaturk2012.pdf> (accessibility date: 7 August 2014).

5. Bevers TB, Anderson BO, Bonaccio E, Buys S, Daly MB, Dempsey PJ. NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis. *J Natl Compr Canc Netw* 2009; 7: 1060-1096. (PMID: 19930975)
6. Seçginli S, Nahcivan NO. Factors associated with breast cancer screening behaviours in a sample of Turkish women: A questionnaire survey. *Int J Nurs Stud* 2006; 43: 161-171. (PMID: 16427965) [\[CrossRef\]](#)
7. Dundar PE, Ozmen D, Ozturk B, Haspolat G, Akyıldız F, Çoban S. The knowledge and attitudes of breast self-examination and mammography in a group of women in a rural area in western Turkey. *BMC Cancer* 2006; 6: 1-9. (PMID: 16504119) [\[CrossRef\]](#)
8. Ekici E, Utkualp N. Behaviors of academics women about breast cancer. *J Breast Health* 2007; 3: 136-139.
9. Güleser GN, Ünalın D, Akyıldız HY. The knowledge and practice of breast self-examination among healthcare workers in Kayseri, Turkey. *Cancer Nursing* 2009; 32: E1-E7. (PMID: 19661791) [\[CrossRef\]](#)
10. Canbulat N, Uzun Ö. Health beliefs and breast cancer screening behaviors among female health workers in Turkey. *Eur J Oncol Nurs* 2008; 12: 148-156. (PMID: 18314391) [\[CrossRef\]](#)
11. Ceber E, Turk M, Ciceklioglu M. The effects of an educational program on knowledge of breast cancer, early detection practices and health beliefs of nurses and midwives. *J Clin Nurs* 2010; 19: 2363-2671. (PMID: 20659208) [\[CrossRef\]](#)
12. Akpınar YY, Baykan Z, Naçar M, Gün İ, Çetinkaya F. Knowledge, attitude about breast cancer and practice of breast cancer screening among female health care professionals: A study from Turkey. *Asian Pacific J Cancer Prev* 2011; 12: 3063-3068. (PMID: 22393990)
13. Haji-Mahmoodi M, Montazeri A, Jarvandi S, Ebrahimi M, Haghighat S, Harirchi I. Breast self-examination: Knowledge, attitudes, and practice among female health care workers in Tehran, Iran. *Breast J* 2002; 8: 222-225. (PMID: 12100114). [\[CrossRef\]](#)
14. Ibrahim NA, Odusanya OO. Knowledge of risk factors, beliefs and practices of female healthcare professionals towards breast cancer in a tertiary institution in Lagos, Nigeria. *BMC Cancer* 2009; 9: 76. (PMID: 19261179). [\[CrossRef\]](#)
15. Cavdar Y, Akyolcu N, Ozbas A, Oztekin D, Ayoglu T, Akyuz N. Determining female physicians' and nurses' practices and attitudes toward breast self-examination in Istanbul, Turkey. *Oncol Nurs Forum* 2007; 34: 1218-1221. (PMID: 18024349) [\[CrossRef\]](#)
16. Champion VL. Instrument refinement for breast cancer screening behaviors. *Nurs Res* 1993; 42: 139-143. (PMID: 8506161) [\[CrossRef\]](#)
17. Karayurt O, Dramalı A. Adaptation of Champion's Health Belief Model Scale for Turkish women and evaluation of the selected variables associated with breast self-examination. *Cancer Nurs* 2007; 30: 69-77. (PMID: 17235224) [\[CrossRef\]](#)
18. Aydın Avcı İ. Factors associated with breast self-examination practices and beliefs in female workers at a Muslim community. *Eur J Oncol Nurs* 2008; 12: 127-133. (PMID: 18242140) [\[CrossRef\]](#)
19. Harirchi I, Mousavi SM, Mohagheghi MA, Mousavi-Jarrahi A, Ebrahimi M, Montazeri A, Rahbar MN. Do knowledge, attitudes and practice of Iranian health care providers meet WHO recommendations on early detection for breast cancer? *Asian Pacific J Cancer Prev* 2009; 11: 57-60. (PMID: 20104977)
20. Alkhasawneh IM. Knowledge and practice of breast cancer screening among Jordanian nurses. *Oncol Nurs Forum* 2007; 34: 1211-1218. (PMID: 18024348) [\[CrossRef\]](#)
21. Shirayzdi SM, Kholashezhadeh G, Neamatzadeh H, Kargar S. Health beliefs and breast cancer screening behaviors among Iranian female health workers. *Asian Pac J Cancer Prev* 2014; 15: 9817-9822. (PMID: 25520111) [\[CrossRef\]](#)
22. Moshfeghi K, Mohammadbeigi A. Comparison the effects of two educational methods on knowledge, attitude and practice of Arak physicians about breast cancer. *Pak J Biol Sci* 2010; 13: 901-905. (PMID: 23350164) [\[CrossRef\]](#)
23. Mishra SI, Bastani R, Huang D, Luce P, Baquet CR. Mammography screening and Pacific Islanders: role of cultural and psychosocial factors. *Journal of Cancer Education* 2007; 22: 32-36. (PMID: 17570806) [\[CrossRef\]](#)
24. Champion VL. Revised susceptibility, benefits, and barriers scale for mammography screening. *Research in Nursing & Health* 1999; 22: 341-348. [\[CrossRef\]](#)
25. Eryılmaz MA, Karahan Ö, Sevinç B, Ay S, Civcik S. Meme kanseri taramalarının etkinliği. *J Breast Health* 2010; 6: 145-149.
26. Greco KE, Nail LM, Kendall J, Cartwright J, Messecar DC. Mammography decision making in older women with a breast cancer family history. *J Nurs Scholarsh* 2010; 42: 348-356. (PMID: 20738746) [\[CrossRef\]](#)
27. Trigoni M, Mahoney MC, Moschandreas J, Tsiftsis D, Koumantakis E, Lionis C. Approaches to breast cancer screening among primary care physicians in rural areas of Crete, Greece. *J Cancer Educ* 2011; 26: 490-496. (PMID: 21221884). [\[CrossRef\]](#)
28. Uncu F, Bilgin N. Knowledge, attitude and behavior of midwives and nurses working in primary health services on breast cancer early diagnosis practices. *J Breast Health* 2011; 7: 167-175.
29. Al-Naggar RA, Isa Z, Shah SA, Chen R, Kadir SYA. Mammography screening: female doctors' attitude and practice in Sana'a, Yemen. *Asian Pac J Cancer Prev* 2009; 10: 743-746. (PMID: 20104962).
30. Sadikoglu G, Ozcakil A, Dogan F, Gokgoz S, Bilge N. Mammography utilization among Turkish women. *Asian Pac J Cancer Prev* 2010; 11: 377-381. (PMID: 20843119).
31. Champion VL, Scott CR. Reliability and validity of breast cancer screening belief scales in African-American women. *Nurs Res* 1997; 46: 331-337. (PMID: 9422052). [\[CrossRef\]](#)
32. Bandura A. Self-efficacy: Toward a unifying theory of behavioral change. *Psychol Rev* 1977; 84: 191-215. (PMID: 847061) [\[CrossRef\]](#)
33. Bandura A. Self-efficacy: The exercise of control. 1997. New York: Freeman.
34. Yarbrough SS, Braden CJ. Utility of Health Belief Model as a guide for explaining or predicting breast cancer screening behaviors. *J Adv Nurs* 2001; 33: 677-688. (PMID: 11298205) [\[CrossRef\]](#)
35. Akhigbe AO, Omuemu VO. Knowledge, attitudes and practice of breast cancer screening among female health workers in a Nigerian urban city. *BMC Cancer* 2009; 9: 1-9. (PMID: 19555506) [\[CrossRef\]](#)
36. Lechner L, Vries H, Offermans N. Participation in a breast cancer screening program: influence of past behavior and determinants on future screening participation. *Prev Med* 1997; 26: 473-482. (PMID: 9245669) [\[CrossRef\]](#)
37. Lerman C, Rimer B, Trock B, Balshem A, Engstrom PF. Factors associated with repeat adherence to breast cancer screening. *Prev Med* 1990; 19: 279-290. (PMID: 2377590) [\[CrossRef\]](#)

# Magnetic Resonance Imaging Guided Vacuum Assisted and Core Needle Biopsies

Fahrettin Kılıç<sup>1</sup>, Abdulkadir Eren<sup>2</sup>, Necmettin Tunç<sup>3</sup>, Mehmet Velidedeoğlu<sup>4</sup>, Selim Bakan<sup>1</sup>, Fatih Aydoğan<sup>4</sup>, Varol Çelik<sup>4</sup>, Ertuğrul Gazioglu<sup>4</sup>, Mehmet Halit Yılmaz<sup>1</sup>

<sup>1</sup>Department of Radiology, İstanbul University Faculty of Medicine, İstanbul, Turkey

<sup>2</sup>Department of Radiology, İstanbul Medipol University, İstanbul, Turkey

<sup>3</sup>Clinic of Radiology, Memorial Hospital, Diyarbakır, Turkey

<sup>4</sup>Department of General Surgery, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

## ABSTRACT

**Objective:** The purpose of this study to present the results of Magnetic resonance imaging (MRI) guided cutting needle biopsy procedures of suspicious breast lesions that can be solely detected on Magnetic resonance (MR) examination.

**Materials and Methods:** The study included 48 patients with 48 lesions which were solely be observed in breast MRI, indistinguishable in ultrasonography and mammography, for MR guided vacuum-assisted cutting needle biopsy and 42 patients with 42 lesions for MR guided cutting needle biopsy for the lesions of the same nature. MR imaging was performed using a 1.5-Tesla MRI device. Acquired MR images were determined and biopsy protocol was performed using computer-aided diagnosis system on the workstation. Vacuum biopsies were performed using 10 G or 12 G automatic biopsy systems, cutting needle biopsy procedures were performed using fully automated 12 G biopsy needle.

**Results:** All biopsy procedures were finalized successfully without major complications. The lesions were 54 mass (60%), 28 were non-mass contrast enhancement (31%) and 8 were foci (9%) in the MR examination. Histopathological evaluation revealed 18 malignant (invasive, in-situ ductal carcinoma and lobular carcinoma), 66 benign (apocrine metaplasia, fibrosis, fibroadenomatoid lesion, sclerosing adenosis, fibrocystic disease and mild-to-severe epithelial proliferation) and 6 high-risk (atypical ductal hyperplasia, intraductal papilloma, radial scar) lesions.

**Conclusion:** Magnetic resonance guided vacuum and cutting needle biopsy methods are successful methods for the evaluation of solely MRI detected suspicious breast lesions. There are several advantages relative to each other in both methods.

**Keywords:** Magnetic resonance imaging, breast neoplasm, image-guided biopsy, vacuum, large core needle

## Introduction

Current modalities that are used to detect breast lesions include ultrasonography, mammography and magnetic resonance imaging (MRI). The sensitivity of MRI in detecting breast lesions is higher as compared to both ultrasonography and mammography (1). Breast MR examination has become an essential and integral component of breast imaging (2). MRI has a high sensitivity in investigating patients at high-risk for breast cancer, in follow-up of breast cancer patients, and in detecting ipsilateral or contralateral disease during preoperative evaluation (3-6). MRI can detect suspicious breast lesions that are neither palpable on clinical examination nor visible by mammography or ultrasonography (5, 7, 8).

Although MRI is a sensitive method for the early detection of breast cancer, its specificity is low despite recent technological advances (9). Suspicious MR-only visible breast lesions that are undetectable by inspection, ultrasonography and mammography should be histologically confirmed. MR-guided needle biopsy, and MR-guided lesion marking followed by excisional surgical biopsy are used for evaluation of such lesions. MR-guided diagnostic biopsies are both less invasive and more suitable in terms of patient comfort as compared to surgical excisional biopsy. According to the European Society of Breast Imaging guideline, MR-guided interventional procedures should be performed for clarification of MR-only visible questionable lesions (5). MR-guided interventional procedures include fine needle biopsy, core-needle biopsy and vacuum assisted biopsy. Vacuum assisted biopsy is superior to fine needle biopsy and core-needle biopsy in terms of providing more material (10). Core-needle biopsy and vacuum assisted biopsy are being increasingly used for histopathologic characterization of suspicious lesions that cannot be detected by clinical examination and can be only monitored by MRI, as significant diagnostic

methods with different advantages over each other. In our study, we aimed to present results of MR-guided vacuum-assisted biopsy and core-needle biopsy performed in our department.

## Material and Methods

### Patient selection and indications for biopsy

90 suspicious breast lesions that were detected with only MRI, in 90 patients at the İstanbul University Faculty of Medicine Department of Radiology between April 2011 and August 2013 were included in the study. Forty-eight patients underwent MR-guided vacuum biopsy and 42 patients underwent core-needle needle biopsy. The study was approved by the İstanbul University Faculty of Medicine Ethical Board, all patients were informed about the procedure and informed consent was obtained from each patient.

Patients who were 18 years or older, with non-palpable suspicious lesions that were only detected by MRI which were evaluated as BI-RADS 4 and 5 according to BI-RADS criteria, and who consented to vacuum biopsy were included in the study. Patients younger than 18 years of age, those who did not consent to participate in the study, those with lesions detected by ultrasonography or mammography, those with palpable lesions, and those who withdrew their consent during the study period were excluded from the study.

### Statistical analysis

The percentage, mean and median values of the data were evaluated by using SPSS (16.0; SPSS, Inc.; Chicago, IL, USA) software.

### MR-Guided Breast Biopsy Techniques

Magnetic resonance imaging during biopsy procedures was performed by using a 1.5-Tesla MRI scanner. The patient was placed in the prone position, breast skin was disinfected with 10% Povidone-iodine at the site of the lesion, and imaging was performed with a 7-channel breast coil that contained compression plates. The compression was applied from both sides of the breast, medial and lateral aspects, in order to reduce artifacts by preventing motion and to enable accurate calculations and stabilization of the breast during needle introduction. Since excessive compression may prevent contrast enhancement, the compression amount was carefully adjusted during stabilization. Bard Vacora (10G) or Suros Atec (12G) biopsy systems were used for vacuum-assisted biopsy. Core-needle needle biopsy procedure was performed by using a 12-G fully automatic biopsy needle.

Interventional procedures began with MR sequences obtained for imaging. First, T1-weighted sagittal images were acquired to verify visibility of the reference points on the compression plates and if the lesion was accessible. Following these steps, T<sub>1</sub>A fast low angle shot (FLASH) 3D sequence (TR / TE, 11 / 5.16, Gap 20, FOV 330, matrix 200x256, frequency direction R> L, bandwidth 150 Hz / Px) images were acquired once before and twice after bolus injection of 0.1 mmol/L per kg of body weight MR contrast agent that was administered via an intravenous catheter. The total imaging time was about 5 minutes.

The received MR images were further evaluated by a computer-aided diagnostic system (CAD; Dynacad, Invivo, Orlando, Florida, USA). The unenhanced images were simultaneously subtracted from contrast images by the workstation. After MR images were obtained following stabilization of the breast, localization of the lesion to be intervened was determined according to reference points within compression plates through the computer-aided diagnosis system. Lesion approach was planned prior to the intervention according to suitable

grid spacing, lesion depth and distance from the skin values provided by the computer, based on lesion localization (medial or lateral). The MR board was removed from the gantry, the patient was re-informed about the process, instructed not to move and the procedure was initiated. Local anesthesia was employed by infiltration of 4-6 cc Prilocaine HCl (Citanest) subcutaneously to the area of interest.

In both vacuum assisted and core-needle biopsy, both the needle and MRI compatible sheath were introduced into the breast together. The cutting needle was removed and a plastic cannula that prevents bleeding out was inserted through the sheath, and control T<sub>1</sub>A FLASH 3D axial MR images were obtained. The sheath and plastic cannula were visualized as thin hypointense artifacts on control MR images, and their localization was confirmed. After determination of appropriate localization, the biopsy procedure was performed with a MRI compatible vacuum biopsy needle that used an ignition system with single insertion, and 6-12 consecutive samples were obtained from the lesion at different points in a clockwise manner. In core-needle biopsy, samples were obtained by 4-5 consecutive introductions with the ignition system. Samples underwent routine histopathologic examination. No major complications occurred during the procedures.

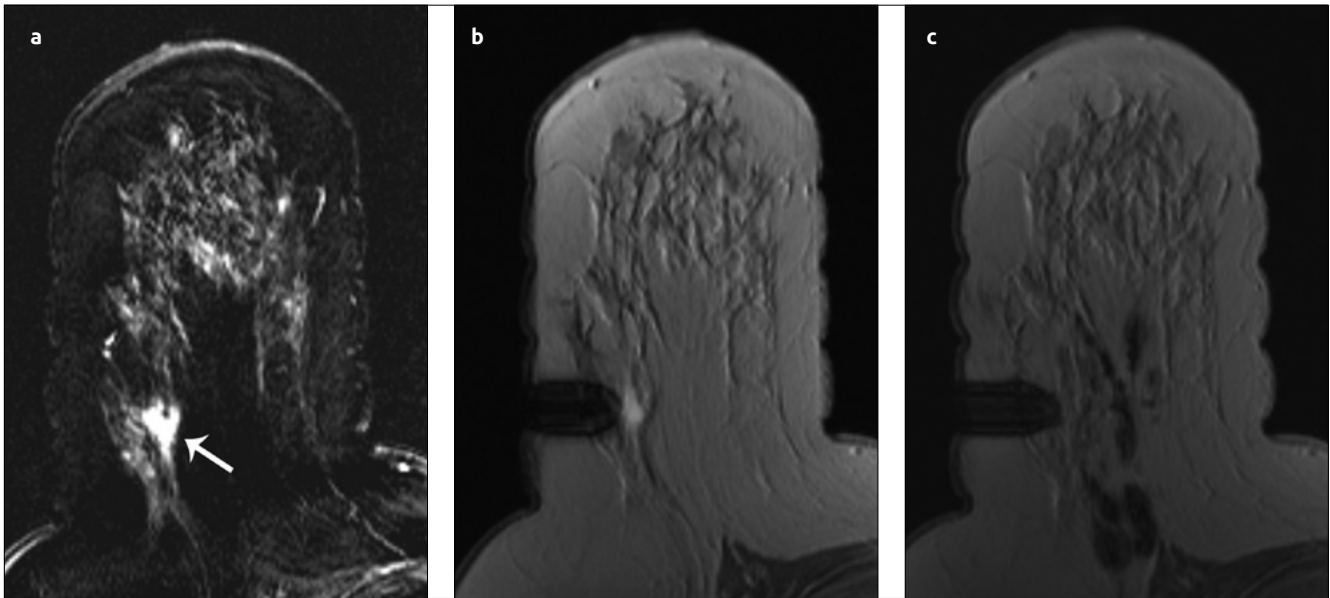
Control T<sub>1</sub>A FLASH 3D axial weighted MR images were obtained following biopsy to verify accuracy of the process, to assess if a second intervention is required, and to check for the presence of a hematoma (Figure 1-3). When the biopsy accuracy was verified, an MRI compatible marker was positioned to the biopsy site, and the procedure was terminated after obtaining control MR images for marker localization. The goal of leaving a marker was to localize the lesion for the surgeon if the pathology showed a malignant lesion, and to locate the lesion on follow-up MR images if the pathology result was benign.

## Results

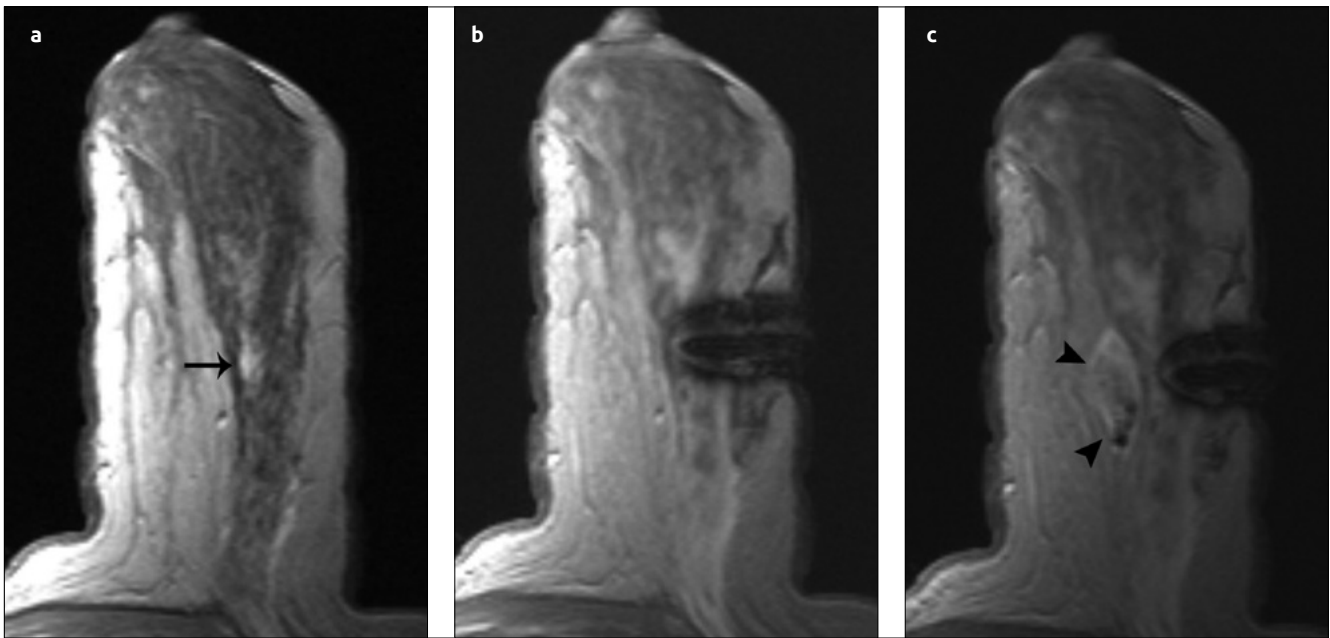
The study included MR-guided biopsies of 90 suspicious breast lesions that can only be detected with MR. Forty-eight patients underwent MR-guided vacuum biopsy and 42 patients underwent core-needle biopsy. The lesions were categorized as benign or malignant according to their histopathologic features on biopsy. The mean age of patients undergoing vacuum biopsy was 45.74 (26-69) years, and was 48.3 (35-56) years in those undergoing core-needle biopsy.

On MR examination, 54 of the 90 lesions were visualized as masses, 28 as non-mass contrast enhancement, and 8 as focus. The median size of the biopsied lesions was 9 mm (4-15 mm) for those undergoing vacuum-assisted biopsy, and was 15 mm (8-22 mm) for those undergoing core-needle biopsy. The median size of all lesions was determined as 12 mm (4-22 mm). The mean procedure duration was 38 minutes (24-69 min) for vacuum assisted biopsies, and was 41 minutes (28-58 min) for core-needle biopsies.

Histopathologic evaluation revealed 10 malignant (20.8%) (invasive and in-situ ductal carcinoma) and 38 benign (79.2%) (apocrine metaplasia, fibrosis, fibroadenomatoid lesion, sclerosing adenosis, fibrocystic disease and mild-moderate-severe epithelial proliferation) lesions among vacuum assisted biopsy samples. Among core-needle biopsies; 8 lesions were malignant (in-situ ductal carcinoma, invasive ductal and lobular carcinoma) (19.4%), 6 were high-risk (atypical ductal hyperplasia, intraductal papilloma, radial scar) (14%), and 28 were benign (fibrocystic changes, sclerosing adenosis, fibroadenoma) (66.6%) lesions.



**Figure 1. a-c.** Core-needle biopsy of a lesion in the right breast of a 35-year-old woman **(a)** The view of an irregular shaped lesion 1cm in diameter that was suspicious for malignancy on subtracted axial contrast-enhanced image (*arrow*) **(b)** The lesion on axial contrast-enhanced T1-weighted image and the adjacent sheath **(c)** Post-biopsy image showing a barely distinguishable lesion and hypointense areas indicating hemorrhage posterior to the lesion. The biopsy revealed invasive ductal carcinoma



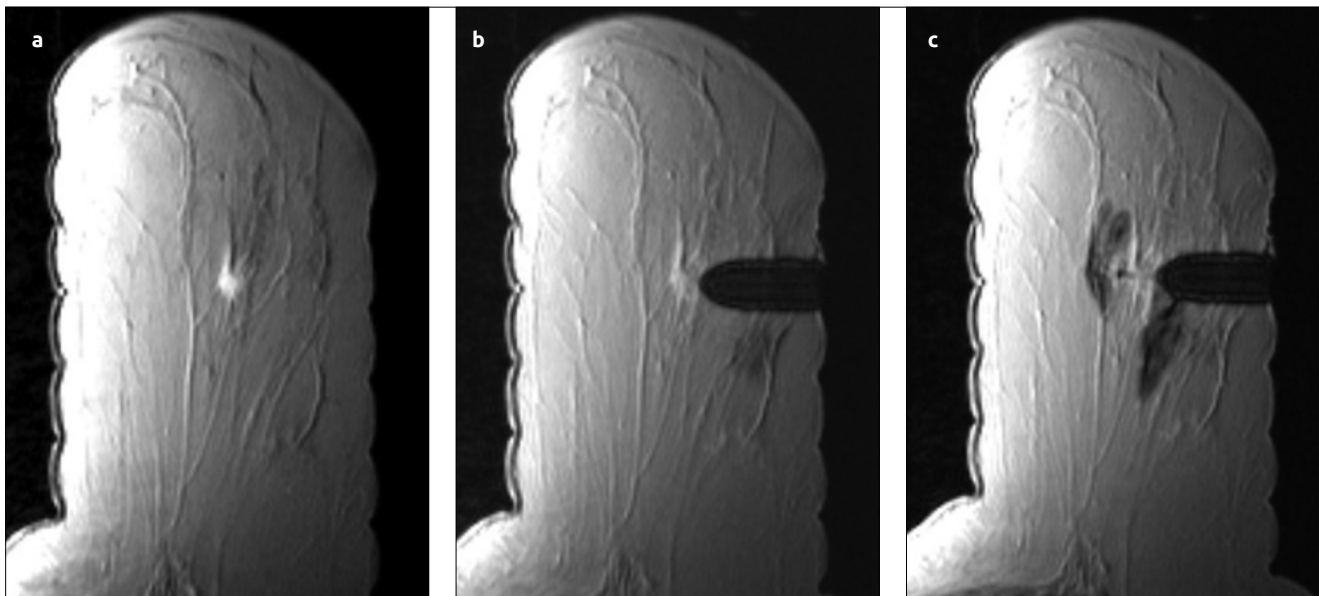
**Figure 2. a-c.** Core-needle biopsy of a lesion in the left breast of a 42-year-old woman **(a)** A 12mm in diameter, non-mass contrast enhancement in the middle outer section of the left breast on axial contrast-enhanced T1-weighted image (*black arrow*) **(b)** Image of the lesion and the adjacent guiding sheath **(c)** Image of a 2cm hematoma just behind the lesion on control imaging after biopsy (*arrowheads*). The biopsy result showed an in-situ ductal carcinoma

Patients diagnosed with malignant and high-risk lesions were referred to medical and/or surgical treatment, and those with benign lesions were recommended to undergo a follow-up MRI or US at 6 months and 1 year. Malignant lesions were treated with breast conserving surgery after MR-guided lesion localization. The results of excisional biopsies of high-risk lesions were compatible with core-needle biopsy results, with no additional malignant findings.

Benign lesions did not show progression and these patients are being monitored by a routine annual follow-up program. A biopsy failure

was considered based on radiology-pathology discordance in 2 patients with core-needle biopsy and 1 patient with vacuum assisted biopsy. Excision was performed in these patients all of which revealed benign findings similar to their biopsy results.

All lesions were visualized on MRI sections during the biopsy procedure. Since the routine breast protocol was not used, and the procedures were performed quickly with rapid decisions based on the CAD system, issues related to contrast wash-out and thus lesion disappearance on control MR cross-sections was not encountered.



**Figure 3. a-c.** Vacuum-assisted biopsy for a lesion of the left breast in a 54-year-old woman **(a)** The view of an irregular bordered, round, nodular lesion 5 mm in diameter on contrast-enhanced T1-weighted axial image of the left breast **(b)** Image of the lesion and the adjacent sheath. Pay attention to the slight contrast washout in the lesion **(c)** The lesion cannot be clearly viewed in control imaging after biopsy along with hypointense hemorrhagic areas around the lesion and the cannula. Biopsy result was reported as invasive ductal carcinoma

## Discussion and Conclusion

Biopsy of occult breast lesions can be performed by MR-guided lesion marking; wire-guidance, Technetium-99 m ROLL (Radio guided occult lesion localization), and by MR-guided radiologic biopsy methods. MR-guided biopsies are both less invasive and more comfortable for the patient as compared to lesion marking and surgical excisional biopsy (11). Obtaining a diagnosis by biopsy prior to lesion marking and excision reduces the number of surgical interventions. If the biopsy result is benign and is consistent with radiologic findings then additional surgical treatment is not required. If the result is malignant then therapeutic procedures may be directly applied. The rate of detecting malignancy after surgical excision of BI-RADS 4-5 lesions varies between 15-40%, while this rate varies between 70-80% in surgical excision after detection of malignancy by radiologic sampling methods (12, 13). Meta-analyses including many studies state that radiologic biopsy methods should be preferred to surgical biopsy, if it can be performed (14, 15).

Vacuum assisted biopsy is less invasive and faster than surgical biopsy and does not cause deformity (16). It has lower risk and morbidity as compared to surgical biopsy, better accuracy than fine needle aspiration biopsy (17), and more sampled tissue than core-needle biopsy (18). It provides bigger and multiple samples in a single entry as compared to fine-needle aspiration and core-needle biopsy. Vacuum assisted biopsy also has a higher technical success rate as compared to fine needle aspiration biopsy.

Other advantages of vacuum biopsy are allowing quick intervention to small lesions (<10 mm) and providing more material for histopathologic evaluation. Core-needle biopsy is superior to fine needle biopsy in terms of providing more material and to vacuum biopsy by being less invasive (19). Carboognin et al. (20) stated that vacuum-assisted biopsy is an effective and reliable method for the diagnosis of MR-only lesions that are non-palpable and smaller than 1 cm. In a study evaluating the efficiency of vacuum-assisted biopsy system and core-needle

biopsy in removing microcalcifications, the failure rate in sampling was reported as 16% for 14G needle as compared to the rate of 4% in 14G vacuum biopsy, and 1% in 11G vacuum biopsy. This valuable study indicated that material sufficiency in vacuum biopsy increased parallel to an increase in needle diameter. The false negativity rate in core-needle biopsy was reported as 8%, while that of vacuum biopsy was determined as 0.67% (21).

Biggest drawback of vacuum biopsy is higher cost as compared to core-needle biopsy (16). The complication rate is higher in vacuum biopsy than other biopsy procedures. Core-needle biopsy is a quite good alternative method to vacuum-assisted biopsy, in case it cannot be performed, with much less complications (22). On the other hand, disadvantages of core-needle biopsy include requirement for multiple insertions for repetitive sampling, decrease in breast tissue with an increase in bloody samples in repeat specimens, and insufficiency in diagnostic sensitivity of calcified lesions, atypical ductal hyperplasia and ductal carcinoma in situ.

Perlet et al. (23) evaluated the histopathologic characteristics of vacuum biopsy on 538 patients, and reported 138 (27%) malignant, 17 (3%), atypical ductal hyperplasia, and 362 (70%) benign findings. Tozaki et al. (24) detected 34 (33%) malignant, 4 (4%) atypical ductal hyperplasia, 5 (5%) flat epithelial atypia, and 59 (58%) benign findings among 100 patients. In the study by Eby and Lehman, (10) 422 (25%) malignant and 1234 (75%) benign findings were detected in 1656 patients.

In our study of 90 patients, 18 (20%) lesions were reported as malignant, 66 (73.3%) as benign, and 6 (6.7%) as high-risk lesions. An indication for operation was detected in 26.7% of cases, and all of these lesions were removed with surgical excision for pathologic evaluation. Our results are comparable with other studies. One reason for the relatively low rate of malignancy in our study was successful utilization of second-look ultrasonography by experienced specialized physicians. Ultrasonography is performed by technicians in most centers except our country. The incidental MR lesions which could be detected by the

guidance of ultrasonography tends to be malignant, and are sampled under ultrasonography guidance (25). With effective use of second-look ultrasonography, the likelihood of ultrasound-guided sampling will increase and the number of cases with MR-guided malignant biopsy will change in favor of the more challenging MRI suspicious but histopathologically benign lesions. Nevertheless, the requirement for specific biopsy indications is evident. A biopsy failure was considered in three patients and the surgical excisions revealed benign lesions similar to the biopsy findings.

The mean duration of vacuum assisted biopsy was reported as 65 min by Malhaire et al. (26), and as 35 min by Tozaki et al. (24). The mean duration of vacuum assisted biopsy was determined as 38 min (24-69 min) in our study, which was in concordance with previous studies. This duration was shortened gradually with increasing patient numbers and experience. Additionally, most of the biopsy procedures were performed with a semi-automatic biopsy system in order to reduce cost, which prolonged duration of the biopsy procedure. The mean biopsy duration for core-needle biopsy was 41 min (28-58 min), and was similar to studies by Liberman et al. (27, 28).

In this study presenting our initial experience, promising results were obtained in computer-aided magnetic resonance imaging guided core-needle and vacuum-assisted biopsy of MR-only visible breast lesions. These methods can be used as an alternative to excisional biopsy for histological diagnosis of lesions detected by MRI, in appropriate cases. It is our opinion that with increasing expertise and accumulating data on follow-up of these patients, these methods will be used more effectively.

**Ethics Committee Approval:** Ethics committee approval was received for this study.

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

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - M.H.Y.; Design - F.K., S.B.; Supervision - M.H.Y., V.Ç., E.G.; Materials - M.V., S.B.; Data Collection and/or Processing - F.K., A.E., N.T.; Analysis and/or Interpretation - F.K.; Literature Review - A.E., N.T.; Writing - F.K., A.E., F.A.; Critical Review - M.H.Y., V.Ç., E.G.

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

**Financial Disclosure:** The authors declared that this study has received no financial support.

## References

- Kuhl C. The current status of breast MR imaging. Part I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical practice. *Radiology* 2007; 244:356-378. (PMID: 17641361) [\[CrossRef\]](#)
- Morris EA. Diagnostic breast MR imaging: current status and future directions. *Magn Reson Imaging Clin N Am* 2010; 18:57-74. (PMID: 19962093) [\[CrossRef\]](#)
- Riedl CC, Ponhold L, Flory D, Weber M, Kroiss R, Wagner T, Fuchsjäger M, Helbich TH. Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and premalignant lesions during surveillance of women at high risk for breast cancer. *Clin Cancer Res* 2007; 13:6144-6152. (PMID: 17947480) [\[CrossRef\]](#)
- Liberman L, Morris EA, Kim CM, Kaplan JB, Abramson AF, Menell JH, Van Zee KJ, Dershaw DD. MR imaging findings in the contralateral breast of women with recently diagnosed breast cancer. *AJR Am J Roentgenol* 2003; 180:333-341. (PMID: 12540428) [\[CrossRef\]](#)
- Viehweg P, Bernerth T, Kiechle M, Buchmann J, Heinig A, Koelbl H, Laniado M, Heywang-Köbrunner SH. MR-guided intervention in women with a family history of breast cancer. *Eur J Radiol* 2006; 57:81-89. (PMID: 16364583) [\[CrossRef\]](#)
- van den Bosch MA, Daniel BL, Pal S, Nowels KW, Birdwell RL, Jeffrey SS, Ikeda DM. MRI-guided needle localization of suspicious breast lesions: results of a freehand technique. *Eur Radiol* 2006; 16:1811-1817. (PMID: 16683117) [\[CrossRef\]](#)
- Morris EA, Liberman L, Dershaw DD, Kaplan JB, LaTrenta LR, Abramson AF, Ballon DJ. Preoperative MR imaging-guided needle localization of breast lesions. *AJR American journal of roentgenology* 2002; 178:1211-1220. (PMID: 11959734) [\[CrossRef\]](#)
- Orel SG, Rosen M, Mies C, Schnall MD. MR imaging-guided 9-gauge vacuum-assisted core-needle breast biopsy: initial experience. *Radiology* 2006; 238:54-61. (PMID: 16304093) [\[CrossRef\]](#)
- Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 2001; 94:153-156. (PMID: 11668491) [\[CrossRef\]](#)
- Eby PR, Lehman CD. Magnetic resonance imaging-guided breast interventions. *Top Magn Reson Imaging* 2008; 19:151-162. (PMID: 18941395) [\[CrossRef\]](#)
- Oxner CR, Vora L, Yim J, Kruper L, Ellenhorn JD. Magnetic resonance imaging-guided breast biopsy in lesions not visualized by mammogram or ultrasound. *Am Surg* 2012; 78:1087-1190. (PMID: 23025947)
- Schueler G, Schueler-Weidekamm C, Helbich TH. Accuracy of ultrasound-guided, large-core needle breast biopsy. *Eur Radiol*. 2008; 18:1761-1773. (PMID: 18414872) [\[CrossRef\]](#)
- Wallis M, Tardivon A, Helbich T, Schreer I. Guidelines from the European Society of Breast Imaging for diagnostic interventional breast procedures. *Eur Radiol* 2007; 17:581-588. (PMID: 17013595) [\[CrossRef\]](#)
- Bruening W, Fontanarosa J, Tipton K, Treadwell JR, Launders J, Schoelles K. Systematic review: comparative effectiveness of core-needle and open surgical biopsy to diagnose breast lesions. *Ann Intern Med* 2010; 152:238-246. (PMID: 20008742) [\[CrossRef\]](#)
- Dahabreh IJ, Wieland LS, Adam GP, Halladay C, Lau J, Trikalinos TA. AHRQ Comparative Effectiveness Reviews. Core Needle and Open Surgical Biopsy for Diagnosis of Breast Lesions: An Update to the 2009 Report. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014.
- Liberman L. Percutaneous image-guided core breast biopsy. *Radiol Clin North Am* 2002; 40:483-500, vi. (PMID: 12117188)
- Wald DS, Weinreb JC, Newstead G, Flyer M, Bose S. MR-guided fine needle aspiration of breast lesions: initial experience. *J Comput Assist Tomogr* 1996; 20:1-8. (PMID: 8576457) [\[CrossRef\]](#)
- Chen X, Lehman CD, Dee KE. MRI-guided breast biopsy: clinical experience with 14-gauge stainless steel core biopsy needle. *AJR Am J Roentgenol* 2004; 182:1075-1180. (PMID: 15039191) [\[CrossRef\]](#)
- Philpotts LE, Hooley RJ, Lee CH. Comparison of automated versus vacuum-assisted biopsy methods for sonographically guided core biopsy of the breast. *AJR Am J Roentgenol* 2003; 180:347-351. (PMID: 12540431) [\[CrossRef\]](#)
- Carbognin G, Girardi V, Brandalise A, Baglio I, Bucci A, Bonetti F, Pozzi Mucelli R. MR-guided vacuum-assisted breast biopsy in the management of incidental enhancing lesions detected by breast MR imaging. *Radiologia Med* 2011; 116:876-885. (PMID: 21293942) [\[CrossRef\]](#)
- Jackman RJ, Rodriguez-Soto J. Breast microcalcifications: retrieval failure at prone stereotactic core and vacuum breast biopsy—frequency, causes, and outcome. *Radiology* 2006; 239:61-70. (PMID: 16567483) [\[CrossRef\]](#)
- Dershaw DD. Equipment, technique, quality assurance, and accreditation for imaging-guided breast biopsy procedures. *Radiol Clin North Am* 2000; 38:773-789, ix. (PMID: 10943277)

23. Perlet C, Heywang-Kobrunner SH, Heinig A, Sittek H, Casselman J, Anderson I, Taourel P. Magnetic resonance-guided, vacuum-assisted breast biopsy: results from a European multicenter study of 538 lesions. *Cancer* 2006; 106:982-990. (PMID: 16456807) [\[CrossRef\]](#)
24. Tozaki M, Yamashiro N, Sakamoto M, Sakamoto N, Mizuuchi N, Fukuma E. Magnetic resonance-guided vacuum-assisted breast biopsy: results in 100 Japanese women. *Jpn J Radiol* 2010; 28:527-533. (PMID: 20799018) [\[CrossRef\]](#)
25. Spick C, Baltzer PA. Diagnostic utility of second-look US for breast lesions identified at MR imaging: systematic review and meta-analysis. *Radiology* 2014; 273:401-409. (PMID: 25119022) [\[CrossRef\]](#)
26. Malhaire C, El Khoury C, Thibault F, Athanasiou A, Petrow P, Ollivier L, Tardivon A. Vacuum-assisted biopsies under MR guidance: results of 72 procedures. *Eur Radiol* 2010; 20:1554-1562. (PMID: 20119729) [\[CrossRef\]](#)
27. Liberman L, Morris EA, Dershaw DD, Thornton CM, Van Zee KJ, Tan LK. Fast MRI-guided vacuum-assisted breast biopsy: initial experience. *AJR Am J Roentgenol* 2003; 181:1283-1293. (PMID: 14573421) [\[CrossRef\]](#)
28. Liberman L, Bracero N, Morris E, Thornton C, Dershaw DD. MRI-guided 9-gauge vacuum-assisted breast biopsy: initial clinical experience. *AJR Am J Roentgenol* 2005; 185:183-93. (PMID: 15972421) [\[CrossRef\]](#)

# Assessment of Risk Factors in Patients who presented to the Outpatient Clinic for Breast Cancer-Related Lymphedema

Aslı Gençay Can, Emel Ekşioğlu, Zeynep Tuba Bahtiyarca, Fatma Aytül Çakıcı

Clinic of Physical Medicine and Rehabilitation, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

## ABSTRACT

**Objective:** Lymphedema is one of the most debilitating outcomes of breast cancer treatment. We aimed to compare the demographic and clinical characteristics of breast cancer patients with and without lymphedema, to assess risk factors for lymphedema, and to evaluate treatment outcomes in lymphedema patients.

**Materials and Methods:** Demographic and clinical characteristics of 84 women with previous surgery for breast cancer who presented to the outpatient clinic between March 2014 and May 2015 were retrospectively extracted from patient records.

**Results:** Upper extremity lymphedema was detected in 34 of 84 patients (40.5%). The mean age, body mass index, the number of positive lymph nodes and the number of patients with postoperative radiotherapy were significantly higher among patients with lymphedema than those without ( $p<0.05$ ). Educational level of patients with lymphedema was significantly lower than the other group ( $p<0.05$ ). The correlation analysis revealed an association between age, educational level, body mass index, tumor stage, number of positive lymph nodes, postoperative radiotherapy and presence of lymphedema. Postoperative radiotherapy was detected as the only independent risk factor by logistic regression analysis. Fourteen out of 26 lymphedema patients were assigned to education, skin care, exercise and compression bandaging therapy. Upper extremity volumes and volume differences were significantly improved after treatment.

**Conclusion:** Advanced age, low educational level, obesity, tumor size, the number of positive lymph nodes and postoperative radiotherapy correlated with the development of lymphedema. Within these factors, postoperative radiotherapy was detected as an independent risk factor for the development of lymphedema. Patient education, skin care, exercise and compression bandage therapy are effective treatment options in breast cancer-related lymphedema.

**Keywords:** Breast cancer, lymphedema, risk factors

## Introduction

Breast cancer is the most common cancer type in women (1, 2). More than 1 million women are diagnosed with breast cancer annually worldwide (3). One in every eight women is expected to develop breast cancer during their lifetime (4).

Although breast cancer treatment is quite effective, post-treatment complications constitute major problems for patients (5). One of the complications occurring after breast cancer treatment is lymphedema and causes serious long-term disability (2, 6). Breast cancer associated upper extremity lymphedema develops because of surgical removal of axillary lymph nodes and/or axillary radiation therapy. The protein-rich lymph fluid accumulates in the interstitial space within the skin-subcutaneous area due to impairment of lymphatic flow and manifests with upper extremity swelling, limitations in mobility, and heaviness (7).

Breast cancer associated lymphedema frequently develops within the first 3 years of treatment, although there is a life-long risk of developing lymphedema (5, 8). Lymphedema incidence in breast cancer patients with axillary lymph node dissection and axillary radiotherapy is reported to be approximately 30% (6, 7). The intensity of lymphedema correlates with the number of axillary lymph nodes removed and the extent of radiation (5). The size of the tumor, advanced age, obesity, immobility, recurring cellulitis and erysipelas also increase the risk (1, 5, 6, 8, 9).

Lymphedema can cause serious physical problems such as limb swelling, pain, limitations in mobility, skin infections and subcutaneous fibrosis. It may impair the patient's quality of life and can develop psychological problems such as anxiety and depression. It can lead to

social isolation and delays in time to return to work. That is why, the prevention, early diagnosis and treatment of lymphedema are significant issues (10).

The diagnosis of lymphedema is usually based on history and physical examination. It is often unilateral (5). Although it can affect the complete arm, it can be localized to the hand, forearm or the upper arm (8). Initially the edema is soft with pitting, while it progresses to a solid edema in time with subcutaneous fibrosis that develops due to inflammation (5). Girth and/or volume measurements are important in physical examination. The most commonly used diagnostic method is girth measurements. Ideally, circumference measurements should be made in the preoperative period and compared with measurements made at regular intervals in the postoperative period, and a difference above 2 cm should be considered as lymphedema. However, since this is not often possible, the postoperative difference between two arm circumferences above 2 cm is regarded as lymphedema. The most accurate measurement technique is the water displacement technique. This technique measures the volume of water that overflows when the arm is submerged in a container filled with water. If the difference between the two arms is greater than 10% or 200 ml then it is regarded as lymphedema (8).

Lymphedema is a disease that can be controlled, but cannot be cured (2). The most accepted lymphedema treatment method is complete decongestive therapy (CDT). CDT is designed to reduce limb volume and to maintain skin health (2, 5, 11). The treatment program consists of two phases of intensive phase (phase 1) and self-management phase (phase 2). The intensive phase is expected to decrease lymphedema volume with a 2-4 week treatment program. The intensive phase includes manual lymph drainage, multi-layer short stretch compression bandaging, patient education, skin care and exercise. The self-management phase is aimed to protect the volume reduction that was obtained in the intensive phase. This phase includes self-massage, compression garments, skin care, patient education and exercise, and lasts for a lifetime (2, 10).

Once lymphedema develops, it requires lifelong monitoring and treatment, without offering cure. Therefore, it is important to inform patients on the issue and prevent lymphedema. This study aimed to compare the demographic and clinical characteristics of breast cancer patients with and without lymphedema, to assess risk factors for lymphedema, and to evaluate treatment outcomes in lymphedema patients.

## Material and Methods

Demographic and clinical characteristics of 84 women with previous surgery for breast cancer who presented to the outpatient lymphedema clinic between March 2014 and May 2015 were retrospectively extracted from patient records. An approval was obtained from the hospital ethics committee.

The demographic characteristics, history on breast cancer and its treatment, co-morbidities, bilateral upper extremity circumference measurements and bilateral upper limb volume values based on girth measurements were evaluated in all patients with breast cancer who presented to our lymphedema outpatient clinics. The circumference measurements were made at the level of the metacarpophalangeal joint, wrist (proximal ulnar styloid), as well as 10 cm proximal and distal to the lateral epicondyle. The volumes were measured by using geometrical volume formulas based on circumference measurements

(12). Patients with at least 2 cm difference between the two upper extremities in at least one level and/or at least a 10% difference between the two upper limb volumes were considered as lymphedema. The stage of lymphedema, severity and follow-up data during follow-up in patients with lymphedema were evaluated. For staging; Stage 1: soft edema with pitting, is reduced temporarily by limb elevation (reversible lymphedema), Stage 2: edema is harder and non-pitting, it does not regress with limb elevation (irreversible lymphedema), Stage 3: lymphedema is advanced, elephantiasis, massive hyperkeratosis and ulceration may occur (irreversible lymphedema). For severity, the lymphedema was considered as mild if the difference between the circumferences between two arms was <3 cm, moderate if between 3-5 cm, and as severe if >5 cm.

At our lymphedema outpatient clinic, patients with breast cancer surgery are evaluated and informed about lymphedema, the issues they should pay attention to in order to prevent lymphedema (eg avoiding trauma, compression, infection, barotrauma, heat and cold, and weight gain) are explained, early symptoms of lymphedema are taught (tightening of clothes, heaviness, redness, numbness and tingling), skin care is emphasized (using neutral pH soap and moisturizer, avoiding cuts, scratches and ingrown nails, keeping fingers and skin folds clean and dry), and the relevant exercises are taught. A multi-layer short-stretch compression bandaging is applied to patients identified to have upper extremity lymphedema as part of phase 1 treatment in addition to the issues mentioned above (education, exercise, skin care). The compression bandage is applied in our clinic on a daily basis and stays on for 23 hours in the extremities. Limb circumference measurements are made on a weekly basis, and the patient is switched to maintenance therapy with compression garment as soon as a plateau in reduction is reached. Patients are recommended to wear a tailor-made, one-piece, class 2-compression garment to the entire arm and hand during the day and asked to remove it during the night. After switching to compression garments, patients are followed-up at our clinic in every 3 months during the first year.

## Statistical analysis

The demographic and clinical characteristics of patients with and without lymphedema had a non-homogeneous distribution, and the inter-group differences were evaluated by the non-parametric Mann-Whitney U test and chi square test. The Spearman correlation coefficient ( $r$ ) was used to determine factors associated with lymphedema.  $r$  0-0.25 was regarded as no correlation, 0.25 to 0.50 as weak-to-moderate correlation, 0.50-0.75 as strong correlation, and 0.75-1 was regarded as a very strong correlation. Logistic regression analysis was made after correlation analysis to identify independent risk factors for lymphedema. The changes in pre- and post- treatment upper extremity volumes and volume differences between the two upper extremities in patients with lymphedema were evaluated with the non-parametric Wilcoxon test. The data were transferred to the electronic environment and were evaluated with the SPSS 13.0 for Windows (SPSS, Inc.; Chicago, IL, USA) software. Statistical significance was set at  $p < 0.05$ .

## Results

The mean age of the 84 patients was  $53.2 \pm 10.2$  years, and their mean duration of education was  $7.2 \pm 4.2$  years. 70 percent of the patients were housewives, 20% were employed and 6% were retired. 73.3% of the patients were married while 26.7% were single. The mean body mass index was  $29.4 \pm 6.5$  kg/m<sup>2</sup>. 86.7% of the patients were right-

handed. 31.7% of patients had hypertension, 15% thyroid disease, 13.3% diabetes mellitus, 6.7% chronic obstructive pulmonary disease, and 1.7% had coronary artery disease. 48.3% of patients underwent left-sided breast surgery, 46.7% had surgery on the right side, and 5% had bilateral disease. Eighty-five percent of patients underwent modified radical mastectomy, while the remaining 15% underwent breast conserving surgery and axillary lymph node dissection. 95% of patients had invasive ductal carcinoma, 3.3% papillary carcinoma and 1.7% tubular carcinoma. In the postoperative period, 71.7% of patients received chemotherapy, 55% received radiotherapy and 58.3% hormonal therapy. The mean period between the date of surgery and the study was  $35.7 \pm 49.3$  months.

Lymphedema was detected in at least one upper extremity in 34 out of 84 patients (40.5%). The average duration of swelling in patients with lymphedema was  $27.8 \pm 39$  months. 33 patients (97.1%) had lymphedema in one upper limb while 1 (2.9%) patient had involvement of both upper extremities. In 19 of the 34 patients with lymphedema (55.9%), lymphedema developed in the dominant upper extremity. Ten patients (29.4%) had stage 1, 22 patients (64.7%) stage 2, and 2 patients (5.9%) had stage 3 lymphedema. The severity of lymphedema was mild in 8 patients (23.5%), moderate in 13 patients (38.2%) and severe in 13 patients (38.2%). None of the patients had a family history of lymphedema. None of the patients had skin involvement (cellulitis, papillomatosis, hyperkeratosis).

The mean age, body mass index, the period between the date of surgery and the study, number of metastatic lymph nodes and number of patients with postoperative radiotherapy was significantly higher in the group with lymphedema than the group without ( $p < 0.05$ ). The mean education duration of patients with lymphedema was significantly lower than that of patients without ( $p < 0.05$ ). There was no difference between the groups in terms of occupation, marital status, dominant limb side, co-morbidity, breast cancer type and stage, breast cancer surgery, number of removed axillary lymph nodes, number of patients with postoperative chemotherapy and hormonal therapy ( $p > 0.05$ ). Demographic and clinical characteristics of patients with and without lymphedema have been presented in detail in Table 1.

Correlation analysis revealed weak-to-moderate association between lymphedema and age, education duration, body mass index, cancer stage, number of positive lymph nodes and postoperative radiotherapy ( $r = 0.25-0.40$ ;  $p < 0.05$ ). There was no correlation between lymphedema and number of removed lymph nodes and postoperative chemotherapy ( $r = 0.14$  to  $0.18$   $p > 0.05$ ). The only independent risk factor was determined as postoperative radiotherapy by logistic regression analysis (OR: 7.09,  $p = 0.04$ ). Correlation analysis and logistic regression analysis results are shown in detail in Table 2 and Table 3, respectively.

Thirteen out of the 34 lymphedema patients (38.2%) did not attend treatment despite recommendations. Four patients (11.8%) did not accept the daily treatment due to transportation problems. Two patients (5.9%) were scheduled for treatment after completion of chemotherapy. Radial, median and ulnar neuropathy due to unilateral lymphedema compression was detected in one patient (2.9%) who was admitted for an inpatient treatment program. Fourteen patients (41.2%) were enrolled in the outpatient treatment program. The multi-layer short-stretch compression bandaging was applied daily for a mean of  $4.5 \pm 1.2$  weeks in patients who received outpatient treatment. The upper extremity volumes with lymphedema, and volume differences between the two upper limbs significantly decreased after

**Table 1. Demographic and clinical features of patients with and without lymphedema**

|                                                           | Patients with Lymphedema<br>(n=34) | Patients Without Lymphedema<br>(n=50) | p      |
|-----------------------------------------------------------|------------------------------------|---------------------------------------|--------|
| Age (year)                                                | $56.6 \pm 10.7$                    | $50.9 \pm 11.5$                       | 0.01*  |
| Education duration (year)                                 | $6.2 \pm 4$                        | $8.2 \pm 4.6$                         | 0.04*  |
| Dominant hand (n, %)                                      |                                    |                                       |        |
| Right                                                     | 28 (%82.3)                         | 42 (%84)                              | 0.72   |
| Left                                                      | 6 (%17.7)                          | 8 (%16)                               |        |
| Occupation (n, %)                                         |                                    |                                       |        |
| Housewife                                                 | 26 (%76.5)                         | 33 (%66)                              | 0.25   |
| Employed                                                  | 6 (%17.6)                          | 11 (%22)                              |        |
| Retired                                                   | 2 (%5.9)                           | 6 (%12)                               |        |
| Marital status (n, %)                                     |                                    |                                       |        |
| Married                                                   | 23 (%67.6)                         | 35 (%70)                              | 0.51   |
| Single                                                    | 11 (%32.4)                         | 15 (%30)                              |        |
| Co-morbidity (n, %)                                       |                                    |                                       |        |
| Hypertension                                              | 12 (%35.3)                         | 18 (%36)                              | 0.06   |
| Diabetes                                                  | 4 (%11.7)                          | 4 (%8)                                | 0.72   |
| COPD                                                      | 2 (%5.9)                           | 2 (%4)                                | 1.00   |
| Thyroid disease                                           | 5 (%14.7)                          | 4 (%8)                                | 0.48   |
| CAD                                                       | 0                                  | 0                                     |        |
| BMI (kg/m <sup>2</sup> )                                  | $31.4 \pm 6.6$                     | $27.5 \pm 5.1$                        | 0.003* |
| Period between the date of surgery and the study (months) | $62.1 \pm 59.6$                    | $18.5 \pm 26.1$                       | 0.000* |
| Breast cancer location (n, %)                             |                                    |                                       |        |
| Right                                                     | 13 (%38.2)                         | 26 (%52)                              | 0.24   |
| Left                                                      | 19 (%55.9)                         | 22 (%44)                              |        |
| Bilateral                                                 | 2 (%5.9)                           | 2 (%4)                                |        |
| Breast cancer type (n, %)                                 |                                    |                                       |        |
| Invasive ductal carcinoma                                 | 33 (%97.1)                         | 48 (%96)                              | 0.66   |
| Tubular carcinoma                                         | 1 (%2.9)                           | 0                                     |        |
| Papillary carcinoma                                       | 0                                  | 2 (%4)                                |        |
| Breast cancer stage (n, %)                                |                                    |                                       |        |
| Stage 1                                                   | 7 (%20.6)                          | 11 (%22)                              | 0.07   |
| Stage 2                                                   | 17 (%50)                           | 20 (%40)                              |        |
| Stage 3                                                   | 10 (%29.4)                         | 17 (%34)                              |        |
| Stage 4                                                   | 0                                  | 2 (%4)                                |        |
| Breast cancer surgery (n, %)                              |                                    |                                       |        |
| MRM                                                       | 30 (%88.3)                         | 44 (%88)                              | 1.00   |
| BCS+ALND                                                  | 4 (%11.7)                          | 6 (%12)                               |        |
| Postoperative CT (n, %)                                   | 29 (%85.3)                         | 35 (%70)                              | 0.11   |
| Postoperative RT (n, %)                                   | 27 (%79.4)                         | 20 (%40)                              | 0.000* |
| Postoperative HT (n, %)                                   | 23 (%67.6)                         | 28 (%56)                              | 0.29   |

COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; BMI: body mass index; MRM: modified radical mastectomy; BCS+ALND: breast conserving surgery+ axillary lymph node dissection; CT: chemotherapy; RT: radiotherapy; HT: hormonotherapy

\*statistically significant

**Table 2. Correlation analysis between the presence of lymphedema and relevant factors**

|                        | <b>r</b><br>(Spearman correlation coefficient) | <b>p</b> |
|------------------------|------------------------------------------------|----------|
| Age                    | 0.27                                           | 0.015*   |
| Education duration     | 0.25                                           | 0.04*    |
| Body mass index        | 0.32                                           | 0.003*   |
| Tumor size             | 0.27                                           | 0.04*    |
| Number of excised LNs  | 0.14                                           | 0.37     |
| Number of positive LNs | 0.37                                           | 0.009*   |
| Postoperative CT       | 0.18                                           | 0.11     |
| Postoperative RT       | 0.40                                           | 0.000*   |

LN: lymph node; CT: chemotherapy; RT: radiotherapy  
\*statistically significant

**Table 3. Logistic regression analysis results on factors related to the presence of lymphedema**

|                       | <b>OR (%95 CI)</b> | <b>p</b> |
|-----------------------|--------------------|----------|
| Age                   | 1.05 (0.98-1.14)   | 0.15     |
| Education duration    | 0.92 (0.74-1.14)   | 0.47     |
| Body mass index       | 1.14 (0.97-1.33)   | 0.09     |
| Tumor size            | 1                  | 0.68     |
| Number of positive LN | 1.21 (0.99-1.48)   | 0.06     |
| Postoperative RT      | 7.09 (1.03-48.94)  | 0.04*    |

LN: lymph node; RT: radiotherapy; OR: Odds ratio; CI: confidence interval  
\*statistically significant

treatment as compared to the pre-treatment values ( $p < 0.05$ ). Pre- and post-treatment evaluations of upper limb volumes are presented in Table 4.

## Discussion and Conclusions

The survival rate in breast cancer is increasing with advances in treatment. However, the morbidity rate is also increasing with the more aggressive treatment approaches (13). Upper extremity lymphedema is one of the most important morbidities developing after breast cancer treatment. In the long term, it poses serious physical and psychological consequences for the patients (11, 14, 15). Lymphedema is a chronic, progressive disease. As there is no cure; its prevention, early diagnosis and treatment are significant (10). We retrospectively evaluated the demographic and clinical characteristics as well as clinical differences between those with and without lymphedema, and response to treatment among breast cancer patients who were evaluated at our lymphedema outpatient clinic, which was established for this particular reason.

The vast majority of patients with and without lymphedema had undergone unilateral breast surgery (92.3% and 94.1%, respectively). In both groups, the most common tumor type was invasive ductal carcinoma (94.1% in those with lymphedema and 96.2% in those

**Table 4. The differences in pre- and post-treatment arm volumes and volume differences between the two arms in patients with lymphedema (mean value  $\pm$  standard deviation)**

|                                        | <b>Pre-treatment</b> | <b>Post-treatment</b> | <b>p</b> |
|----------------------------------------|----------------------|-----------------------|----------|
| Arm volume with lymphedema (mL)        | 184.9 $\pm$ 44.3     | 163.9 $\pm$ 41.8      | 0.001*   |
| Volume difference between two arms (%) | 32.4 $\pm$ 22.5      | 20.2 $\pm$ 18.6       | 0.000*   |

\*statistically significant

without). The rate of patients with modified radical mastectomy was 84.6% in the group of patients with lymphedema, while it was 85.3% in patients without lymphedema. The remaining patients in both groups had undergone breast conserving surgery and axillary lymph node dissection. Patients with and without lymphedema were similar in terms of demographic and clinical characteristics.

In the literature, the development of breast cancer related lymphedema was associated with advanced age, lower educational level, tumor size (tumor stage), the number of removed lymph nodes, the number of positive lymph nodes, and recurrent episodes of cellulitis (1, 5, 6, 8, 9). The mean age of patients and the number of positive lymph nodes in patients with lymphedema was significantly higher in our study as compared to those without lymphedema. Educational level was significantly lower in patients with lymphedema. The most common tumor stage was stage 2 in both groups, and there was no significant difference between the two groups in terms of tumor stage or the number of lymph nodes removed. There were no history or physical findings of cellulitis in both groups. Compatible with the literature; older age, lower education level, advanced tumor stage and the number of positive lymph nodes were associated with the development of lymphedema. The logistic regression analysis revealed that none of these factors was independent risk factors. This result was attributed to the limited number of patients in our study.

Currently, the correlation between body mass index and lymphedema is well defined (16, 17). A high body mass index leads to chronic venous insufficiency and impair lymphatic return, thereby result in lymphedema (16). A body mass index above 30 kg/m<sup>2</sup> increases the risk of lymphedema (18). In our study, the mean body mass index of patients with lymphedema was above 30 kg/m<sup>2</sup> and was significantly higher than those without lymphedema. In accordance with the literature, a positive correlation was identified between the development of lymphedema and body mass index. However, it was not identified as an independent risk factor on logistic regression analysis. The limited number of patients, as mentioned earlier, may have led to such a result.

Breast cancer related upper extremity lymphedema is associated with breast cancer treatment (5, 8). In the literature, the prevalence of lymphedema following axillary lymphadenectomy and axillary radiotherapy is reported as approximately 30%, although varying between 24% and 49%. The difference in rates are related to the extent of axillary surgery and radiotherapy, different assessment methods, lack of standardization in diagnostic criteria, and differences in postoperative follow-up periods (6, 7, 19). In our study, 40.5% of patients who presented to our clinic with breast cancer were found to have upper extremity lymphedema. This rate in our study is consistent with the literature (6, 7).

Although there is a lifetime risk of developing breast cancer related lymphedema, approximately 80% of the cases occur within the first 3 years after treatment (5, 8, 19). In our study, lymphedema was detected at a mean of 5 years after breast surgery. This difference was thought to result from being overlooked by clinicians, lack of awareness among patients and limited number of lymphedema treatment centers in our country that lead to delays in both diagnosis and treatment of such patients.

Axillary radiotherapy may cause fibrosis in the lymph vessels and lymph nodes, disrupt lymphatic flow, and may trigger lymphedema (6). Similarly, postoperative chemotherapy may increase extracellular fluid volume with chronic inflammation, increase lymphatic load and result in lymphedema (20, 21). In our study, the rate of patients receiving postoperative radiotherapy was significantly higher in patients with lymphedema than those without. The rate of receiving chemotherapy was also higher in patients with lymphedema, but the difference was not statistically significant. Both postoperative radiotherapy and chemotherapy were associated with lymphedema, but only postoperative radiotherapy was determined as an independent risk factor in logistic regression analysis.

Complete decongestive therapy is the most accepted and widely used method in lymphedema treatment (22, 23). The most important component of CDT phase 1 treatment is short-stretch compression bandaging. Several studies showed that efficient and effective results could be obtained in mild and moderate lymphedema without MLD component (22, 24, 25). In our study, 14 patients were treated with phase 1 components including education, skin care, exercise, and daily multi-layer short-stretch compression bandaging. After an average of 4.5 weeks of treatment, the differences between the two upper-extremity circumferences and volumes significantly declined as compared to pre-treatment values. In their study on 35 patients with breast cancer related lymphedema, Johansson et al. (25) applied compression bandage and manual lymphatic drainage in 17, while applying compression bandaging alone in 18 patients for 3 weeks. At the end of treatment, a 26% volume reduction was achieved in patients with compression bandaging alone. They determined that there was a slightly increase in volume decrease with the addition of MLD to treatment, and stated that the maximum volume reduction in CBT treatment was achieved by the application of compression bandaging alone (25). In our study, the patient's upper limb volumes were decreased by 18.6% at the end of treatment. The low reduction rate in our study as compared to Johansson et al. (25) was attributed to the small number of patients and differences in patient assessment methods. Andersen et al. (22) used Class 2 compression garments, education, skin care and exercise without MLD and compression bandaging in 21 patients with breast cancer-related unilateral lymphedema, while they applied additional MLD to the other 21 patients. The limb volumes significantly decreased in both groups at the end of treatment; nevertheless, they emphasized that the addition of MLD did not have a significant contribution to volume reduction (22). We have also achieved a significant decline in our patients by compression therapy alone, without MLD component.

Patients treated for breast cancer have a life-long risk for lymphedema. Advanced age, lower education level, obesity, tumor size, number of positive lymph nodes and postoperative radiotherapy were detected as factors associated with lymphedema. Postoperative radiotherapy was identified as an independent risk factor for the development of lymphedema. Acceptable results are obtained in lymphedema treatment with patient education, skin care, exercise and compression therapy.

**Ethics Committee Approval:** Ethics committee approval was received for this study.

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

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - A.G.C., E.E.; Design - A.G.C., Z.T.B.; Supervision - F.A.Ç., E.E.; Funding - Z.T.B., A.G.C.; Materials - Z.T.B., A.G.C.; Data Collection and/or Processing - A.G.C., Z.T.B., E.E., F.A.Ç.; Analysis and/or Interpretation - A.G.C.; Literature Review - A.G.C.; Writing - A.G.C.; Critical Review - A.G.C.

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

**Financial Disclosure:** The authors declared that this study has received no financial support.

## References

- Marcos AL, Gaaied AE, Ayed FB, Hassen SB, Zervoudis S, Navrozoglou I, Pechlivani F, Iatrakis G. Lymphedema of the arm after surgery for breast cancer: new physiotherapy. *Clin Exp Obs Gynecol* 2012; 39:483-488. (PMID: 23444749)
- Leal NF, Carrara HH, Vieira KF, Ferreira CH. Physiotherapy treatments for breast cancer-related lymphedema: a literature review. *Rev Lat Am Enfermagem* 2009; 17:730-736. (PMID: 19967225) [CrossRef]
- Mahamaneerat WK, Shyu CR, Stewart BR, Armer JM. Breast cancer treatment, BMI, post-op swelling/lymphoedema. *J Lymphoedema* 2008; 3:38-44. (PMID: 20657749)
- Megens A, Harris SR. Physical therapist management of lymphedema following treatment for breast cancer: a critical review of its effectiveness. *Phys Ther* 1998; 78:1302-1311. (PMID: 9859949)
- Tiwari P, Coriddi M, Salani R, Povoski SP. Breast and gynecologic cancer-related extremity lymphedema: a review of diagnostic modalities and management options. *World J Surg Oncol* 2013; 11:237. (PMID: 24053624) [CrossRef]
- de Rezende LF, Rocha AVR, Gomes CS. Risk factors for breast cancer related lymphedema. *J Vasc Bras* 2010; 9:233-238.
- Kim L, Jeon JY, Sung IY, Jeong SY, Do JH, Kim HJ. Prediction of treatment outcome with bioimpedance measurements in breast cancer related lymphedema patients. *Ann Rehabil Med* 2011; 35:687-693 (PMID: 22506192) [CrossRef]
- Golshan M, Smith B. Prevention and management of arm lymphedema in the patient with breast cancer. *J Support Oncol* 2006; 4:381-386. (PMID: 17004511)
- Sagen A, Karesen R, Risberg MA. Physical activity for the affected limb and arm lymphedema after breast cancer surgery. A prospective, randomized controlled trial with two years follow-up. *Acta Oncol* 2009; 48:1102-1110. (PMID: 19863217) [CrossRef]
- Witty MF, Larouche K. Treatment of cancer-related secondary lymphedema. *ETMIS* 2011; 7:14-17.
- Szuba A, Achalu R, Rockson SG. Decongestive lymphatic therapy for patients with breast carcinoma-associated lymphedema. A randomized, prospective study of a role for adjunctive intermittent pneumatic compression. *Cancer* 2002; 95:2260-2267. (PMID: 12436430) [CrossRef]
- Sander AP, Hajer NM, Hemenway K, Miller AC. Upper-extremity volume measurements in women with lymphedema: a comparison of measurements obtained via water displacement with geometrically determined volume. *Phys Ther* 2002; 82:1201-1212. (PMID: 1244879)
- Paiva DMF, Rodrigues VO, Cesca MG, Palma PV, Leite ICG. Prevalence of lymphedema in women undergoing treatment for breast cancer in a referral center in southeastern Brazil. *BMC Womens Health* 2013; 13:6. (PMID: 23406386) [CrossRef]

14. Martin ML, Hernandez MA, Avendano C, Rodriguez F, Martinez H. Manual lymphatic drainage therapy in patients with breast cancer related lymphedema. *BMC Cancer* 2011; 11:94. (PMID: 21392372) [\[CrossRef\]](#)
15. Petrek JA, Heelan MC. Incidence of breast carcinoma-related lymphedema. *Cancer* 1998; 83:2776-2781. (PMID: 9874397) [\[CrossRef\]](#)
16. Wilkins C, Swain G, Cooke C. Facing up to the obesity crisis: outcomes of a bariatric lymphoedema clinic. *Journal of Lymphedema* 2014; 9:27-29.
17. Shahpar H, Atieh A, Maryam A, Fatemeh HS, Massoome N, Mandana E, Masud Y, Reza MH, Esmail AM. Risk factors of lymph edema in breast cancer patients. *Int J Breast Cancer* 2013; 2013:641818. (PMID: 23862068)
18. Helyer LK, Varnic M, Le LW, Leong W, McCready D. Obesity is a risk factor for developing postoperative lymphedema in breast cancer patients. *Breast J* 2010; 16:48-54. (PMID: 19889169) [\[CrossRef\]](#)
19. Tambour M, Tange B, Christensen R, Gram B. Effect of physical therapy on breast cancer related lymphedema: protocol for a multicenter, randomized, single-blind, equivalence trial. *BMC Cancer* 2014; 14:239. (PMID: 24708851) [\[CrossRef\]](#)
20. Lee MJ, Beith J, Ward L, Kilbreath S. Lymphedema following taxane-based chemotherapy in women with early breast cancer. *Lymphat Res Biol* 2014; 12:282-288. (PMID: 25411764) [\[CrossRef\]](#)
21. Jung SY, Shin KH, Kim M, Chung SH, Lee S, Kang HS, Lee ES, Kwon Y, Lee KS, Park IH, Ro J. Treatment factor affecting breast cancer-related lymphedema after systemic chemotherapy and radiotherapy in stage II/III breast cancer patients. *Breast Cancer Res Treat* 2014; 148:91-98. (PMID: 25253173) [\[CrossRef\]](#)
22. Andersen L, Hojris I, Erlandsen M, Andersen J. Treatment of breast cancer-related lymphedema with or without manual lymphatic drainage-a randomized study. *Acta Oncol* 2000; 39:399-405. (PMID: 10987238) [\[CrossRef\]](#)
23. Popovic-Petrovic S, Nedeljkovic M, Petrovic T, Vasovic M. Physical treatment of secondary lymphedema of the arm in breast cancer patients. *Arch Oncol* 2002; 10:261-262. [\[CrossRef\]](#)
24. Huang TW, Tseng SH, Lin CC, Bai CH, Chen CS, Hung CS, Wu CH, Tam KW. Effects of manual lymphatic drainage on breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials. *World J Surg Oncol* 2013; 11:15. (PMID: 23347817) [\[CrossRef\]](#)
25. Johansson SK, Albertsson M, Ingvar C, Ekdahl C. Effects of compression bandaging with or without manual lymph drainage treatment in patients with postoperative arm lymphedema. *Lymphology* 1999; 32:103-110. (PMID: 10494522)

# Efficacy of Sonoelastography in Distinguishing Benign from Malignant Breast Masses

Adile Balçık<sup>1</sup>, Ahmet Veysel Polat<sup>2</sup>, İlkey Koray Bayrak<sup>2</sup>, Ayfer Kamalı Polat<sup>3</sup>

<sup>1</sup>Clinic of Radiology, Afyonkarahisar State Hospital, Afyonkarahisar, Turkey

<sup>2</sup>Department of Radiology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey

<sup>3</sup>Department of General Surgery, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey

## ABSTRACT

**Objective:** The study aimed to evaluate the influence of sonoelastographic strain ratio in distinguishing benign from malignant breast masses.

**Materials and Methods:** Patients who were referred for diagnostic biopsy of a breast mass were examined by ultrasound and sonoelastography prior to percutaneous biopsy. Sonoelastography was performed twice by the same observer in the same session. The strain ratios (SR) were calculated for both measurements as well as the mean strain ratio. Results were compared with histopathologic findings. For each strain ratio, a threshold value was determined using a ROC analysis for the differentiation of benign and malignant masses.

**Results:** After histopathological examination of 135 mass lesions in 132 female patients (mean age 48±12 years), 65 masses were diagnosed as benign and 70 as malignant. According to the Tsukuba classification with 5 scores; 44 of 65 benign masses had scores of either 1 or 2 while 56 of 70 malignant lesions had scores of either 4 or 5. No benign lesion was classified as score 5, and no malignant lesion as score 1. The mean cut-off in the two ROC measurements in distinguishing benign from malignant lesions was calculated as 4.52. When a threshold value of 4.52 was used for the mean strain ratio: the sensitivity, specificity, PPV, NPV, and accuracy rates were determined as 85.5%, 84.8%, 85.5%, 84.8% and 85.2%, respectively.

**Conclusion:** The threshold value for strain ratio in the differentiation of benign and malignant masses was detected as 4.52, and a significant intra-observer difference was not observed in this study. The diagnostic value of sonoelastography in distinguishing benign from malignant breast masses was higher in comparison to conventional ultrasound.

**Keywords:** Breast neoplasm, ultrasound, sonoelastography

## Introduction

Breast ultrasound (US) is a non-invasive, inexpensive modality without ionizing radiation. It is useful in the radiologic differentiation of solid-cystic lesions detected on mammography, especially in dense breasts. Although ultrasound has a high diagnostic accuracy, it has some limitations in distinguishing benign from malignant tumors. The lesions that cannot be differentiated as either benign or malignant by ultrasound require biopsy in order to obtain histopathologic diagnosis, 60-95% of which are diagnosed as benign. This leads to unnecessary disruption of patient comfort, patient anxiety and financial loss. That is why, noninvasive methods that can increase the sensitivity and specificity of mammography and ultrasound thereby reduce unnecessary biopsies of benign lesions are required (1-3).

Methods to improve the diagnostic specificity and accuracy of ultrasound without affecting its sensitivity in the evaluation of breast lesions have been investigated. Sonoelastography is a non-invasive ultrasound technique determining the stiffness of lesions and the probability of malignancy for that lesion. Malignant tissues are generally harder than benign tissues due to the diffuse desmoplastic reaction they contain. This method evaluates compressibility of the length between two specified points. Malignant lesions are usually harder in structure that represent as non-compressible lesions, while normal tissues with soft character and benign nature are compressible. This distance changes that represent compressibility is called "elastography" (4-7).

The elasticity of the breast lesion is compared with that of the normal surrounding tissue for breast sonoelastography, and is scored from 1 to 5. Since this scoring is a subjective method, an index known as the "strain ratio" is defined for semiquantitative determination of tissue stiffness. In addition to these, it has been determined that the fat tissue in the breast, normal glandular tissue, fibrous tissue, ductal carcinoma in situ and invasive ductal carcinoma all have different elastic modules and strain ratios (8).

*This study was presented at the 33<sup>rd</sup> National Radiology Congress, 07-11 November 2012, Antalya, Turkey.*

**Address for Correspondence:**

Ahmet Veysel Polat e-mail: veyselp@hotmail.com

Received: 17.11.2015  
Accepted: 21.11.2015

The aim of this study was to evaluate the contribution of elastographic strain ratios in the distinction between benign and malignant breast masses.

## Material and Methods

Our study was conducted at Ondokuz Mayıs University Faculty of Medicine Department of Radiology between October 2011-July 2013. A faculty ethics committee approval was obtained for this prospective study as well as informed consents from all participants. Patients who were referred for diagnostic biopsy of a breast mass were prospectively evaluated. The same physician performed the conventional ultrasound and sonoelastography evaluations prior to biopsy in all patients. The sonoelastography examination was held twice in the same session by the same radiologist and strain ratios were calculated for each study in order to evaluate intra observer agreement. Conventional ultrasound findings, both strain ratios and the mean strain ratio were recorded and compared with histopathologic results.

Ultrasound examinations were performed in a fairly low lightning ultrasound room. Patients were examined in the supine position. The examination was performed by using a digital ultrasound elastography device (Aplio XG SSA-790, Toshiba Medical Systems Corporation, Otawara, Japan) equipped with real-time elastography software and a 8-MHz linear transducer.

Initially conventional ultrasound was performed in all patients to assess the size, shape, border characteristics, posterior acoustic features, echogenicity, internal structure, and the presence of calcification in the lesion; the images of these features were recorded and lesions were classified according to the ultrasound 'breast imaging, report and data systems' (BI-RADS) categories. According to BI-RADS categorization, the threshold for benign and malignant distinction was considered as BI-RADS 3-4.

Sonoelastography measurements were performed immediately after conventional ultrasound. The ultrasound transducer was placed on the breast mass in the supine position, parallel to the long axis of the mass. The operator placed sonoelastography box over the lesion to be evaluated after obtaining the complete ultrasonographic view of the breast lesion on the screen, and performed 5-6 consecutive compression-decompressions in the anteroposterior direction. In eight lesions, the long axis of the mass was greater than the probe length therefore, the assessment was performed in a way to include the majority of the lesion

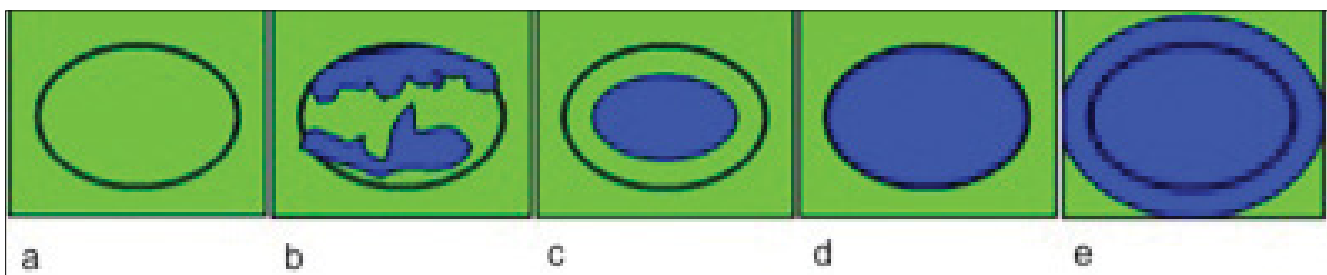
and some normal adipose tissue. During the probe movement, gray-scale ultrasound images of the mass were simultaneously visualized on the sonography screen. The ultrasound device automatically produced the sonoelastography images by comparing the two adjacent compression and relaxation frames that were obtained with continuous probe movement. The compression and relaxation curves were seen as curves above and below the base line on the elastography screen, respectively. The strain pattern in the resulting sonoelastography image was visually scored according to the Tsukuba scoring method defined by Itoh et al. (9) (Figure 1). Then, the strain ratio was calculated for the specified lesion. The strain ratio evaluation was made in the most appropriate relaxation curve with a sinusoidal shape. The strain ratio was obtained by comparing strain values of the lesion and normal tissue at a similar depth. The mean strain ratio was determined in the region of interest (ROI) that was depicted by the letter A placed over the mass. The ROI was drawn in a way that covered the entire lesion considering the areas with different firmness and presence of calcifications within the mass. In lesions that had a greater axis than the probe, the ROI was placed so that the mass can be covered almost entirely. Then, the letter B was placed in the adipose tissue adjacent to the ROI. The compression-decompression process and strain ratio calculation was repeated twice for each patient. Finally, the strain ratio that reflected mass stiffness was calculated by the following formula: Strain ratio = B / A (Figure 2).

All patients underwent ultrasound guided 14G tru-cut biopsy on the same day after sonoelastography examination.

142 patients with 145 mass lesions were evaluated with sonoelastography. Eight patients in whom the histopathologic examination results could not be obtained, and two patients with insufficient and unreliable histopathologic diagnoses (non-diagnostic) were excluded from the study. Overall, 135 solid lesions in 132 female patients formed the basis for the study group.

## Statistical analysis

All statistical analyzes were performed with Statistical Package for the Social Sciences version 15.0 software package (SPSS, Inc.; Chicago, IL, USA). The quantitative data were compared by using the Student-t test and the qualitative data by the chi-square test. An ROC analysis was used to determine the optimal threshold value for strain ratio. Cross-table tests were performed to evaluate the diagnostic value of conventional ultrasound and sonoelastography by comparing their findings with the histopathologic results. Diagnostic sensitivity, specificity, positive predictive value, negative predictive value, and accuracy



**Figure 1. a-e.** According to the Tsukuba scoring system (a) ES-1 lesion coded entirely in green, indicates that the mass is soft (b) ES 2-mass coded in blue and green mosaic, indicates the heterogeneous distribution of soft-hard internal structure. c. ES3-mass is coded in blue in the center surrounded by green color, indicating that the central lesion is hard while has a softer outer structure (d) ES4-mass that is completely blue indicating that it is completely rigid and has a firm internal structure (e) ES5-blue coding on the mass and surrounding adjacent tissue covering an area larger than the size of the mass indicating rigid internal structure due to the desmoplastic reaction in both the mass and the surrounding soft tissue (9)

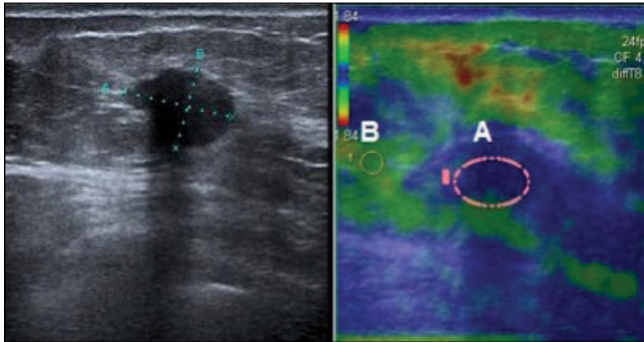
rates were calculated. The agreement between two strain ratios measured by the same person was evaluated by the concordance correlation coefficient statistics. The concordance of the two strain ratios in terms of differentiating malignancies was evaluated by the  $\kappa$  test statistic. According to Landis and Koch the kappa value;

<0 No agreement  
 0.0 - 0.20 Slight agreement  
 0.21 - 0.40 Fair agreement  
 0.41 - 0.60 Moderate agreement  
 0.61 - 0.80 Substantial agreement  
 0.81 - 1.00 Almost perfect agreement (10).

Quantitative data were expressed as ( $AO \pm SD$ ). A p value less than 0.05 was considered as statistically significant at the 95% confidence interval.

## Results

The mean patient age was  $48 \pm 12$  years (range 16-82 years). One hundred thirty patients had one lesion each, one patient had 2, and one had 3 lesions yielding a total of 135 breast masses. The mean maximum diameter in the study group was  $18 \pm 8$  mm (range 6-50 mm), and the mean minimum diameter was  $12 \pm 6$  mm (range 3-40 mm).



**Figure 2. a, b.** The method of strain ratio measurement. Strain ratio = Mean strain in breast adipose tissue (B) / mean strain in the mass (A)

**Table 1. Histopathology results of benign lesions**

| Histopathology Result          | Benign (n=65) |
|--------------------------------|---------------|
| Fibroadenoma                   | 41 (58.4%)    |
| Fibrotic breast tissue         | 7 (10.8%)     |
| Intraductal papilloma          | 6 (9.2%)      |
| Fibrocystic change             | 3 (4.6%)      |
| Fat necrosis                   | 2 (3.1%)      |
| Intramammary lymph node        | 1 (1.5%)      |
| Lactational adenoma            | 1 (1.5%)      |
| Congested breast tissue        | 1 (1.5%)      |
| Benign phyllodes tumor         | 1 (1.5%)      |
| Adenosis + apocrine metaplasia | 1 (1.5%)      |
| Subareolar abscess             | 1 (1.5%)      |

Eighty lesions were localized in the right and 55 in the left breast. Thirty-seven of the masses in the right breast were benign and 43 were malignant, while 28 of the masses in the left breast were benign and 27 were malignant. There were no significant differences between the right and left breasts in terms of malignancy.

Histopathologic examination revealed 65 benign masses, while 70 were diagnosed as malignant (Table 1, 2).

Ultrasound findings were classified according to BI-RADS categorization. Since biopsy is not indicated for BI-RADS 2 lesions and only patients who underwent biopsy were included in our study, they were not represented in this study. Within BIRADS 3 lesions, 1 was diagnosed as malignant and one BI-RADS 5 lesion was diagnosed as benign (Table 3).

## Sonoelastography results

According to the Tsukuba scoring system consisting of five categories, 44 of 65 benign lesions were Score 1 or 2. On the other hand, 56 of the 70 malignant lesions had a score of 4 or 5. There were no benign lesions within Score 5 lesions, or no malignant lesions within those with Score 1 (Table 4).

The mean strain ratio in both measurements and the overall mean were  $2.8 \pm 1.7$ ,  $3.07 \pm 1.8$  and  $2.9 \pm 1.7$  for benign masses, and  $8.4 \pm 4.2$ ,  $8.7 \pm 3.9$  and  $8.6 \pm 3.8$  for malignant lesions, respectively (Figure 3, 4).

The mean strain ratios of malignant masses were significantly higher than benign masses in all three evaluations ( $p < 0.0001$ ).

**Table 2. Histopathology results of malignant lesions**

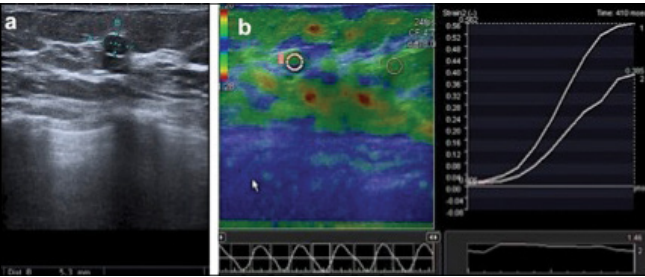
| Histopathology Result                                | Malignant (n=70) |
|------------------------------------------------------|------------------|
| Invasive ductal carcinoma                            | 63 (88.6%)       |
| Granulocytic sarcoma                                 | 1 (1.4%)         |
| Invasive papillary carcinoma                         | 1 (1.4%)         |
| Malignant phyllodes tumor                            | 1 (1.4%)         |
| Invasive lobular carcinoma                           | 1 (1.4%)         |
| Ductal carcinoma in situ                             | 1 (1.4%)         |
| Mucinous carcinoma                                   | 1 (1.4%)         |
| Breast carcinoma with neuroendocrine differentiation | 1 (1.4%)         |

**Table 3. Histopathologic results according to BI-RADS categorization**

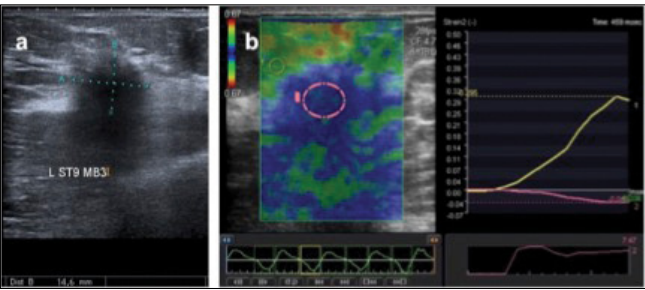
|                                                  | BI-RADS 3 | BI-RADS 4 | BI-RADS 5 |
|--------------------------------------------------|-----------|-----------|-----------|
| Benign                                           | 36        | 28        | 1         |
| Malignant                                        | 1         | 23        | 46        |
| Total                                            | 37        | 51        | 47        |
| BI-RADS: Breast imaging, report and data systems |           |           |           |

Table 4. Histopathologic results according to Tsukuba Scoring

|           | Score 1  | Score 2  | Score 3  | Score 4  | Score 5  | Total |
|-----------|----------|----------|----------|----------|----------|-------|
| Benign    | 21 (%32) | 23 (%35) | 15 (%23) | 6 (%9)   | 0 (%0)   | 65    |
| Malignant | 0 (%0)   | 3 (%4)   | 11 (%16) | 25 (%36) | 31 (%44) | 70    |
| Total     | 21 (%16) | 26 (%19) | 26 (%19) | 31 (%23) | 31 (%23) | 135   |

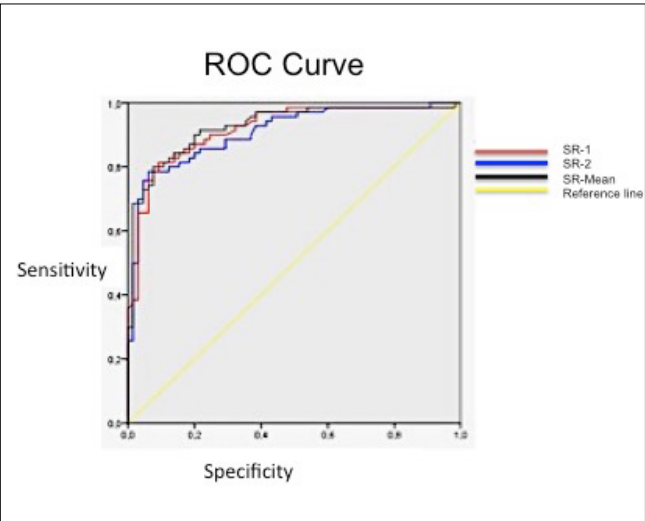


**Figure 3. a, b.** A 60-year-old female patient (a) Gray-scale ultrasound revealed a 8x5 mm in size, well-circumscribed, homogeneous mass in the right breast at 3 radius within 2 cm of the nipple, BI-RADS 3 (b) The strain ratio on elastography is measured as 1.46 with an elasticity score of 1. This mass was considered as benign due to sonoelastography features and was diagnosed as fibroadenoma on histopathologic evaluation



**Figure 4. a, b.** A 52-year-old female patient (a) Gray-scale ultrasound showing a 20x15 mm in size, irregular bordered, heterogeneous lesion with posterior acoustic shadowing mass evaluated as BI-RADS 5 in the left breast at 9 radius within 3 cm from the nipple (b) Elastogram strain ratio was measured as 7.47 with an elasticity score of 5. This mas was evaluated as malignant by its sonoelastography features and was diagnosed as invasive ductal carcinoma after histopathologic examination

For the first measurement, the threshold value in distinction between benign and malignant masses was found to be 4.60. When this threshold was used; the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were detected as 84.1%, 83.3%, 84.1% and 83.3%, respectively. The threshold value in distinction between benign and malignant masses was found to be 4.65 for the second measurement. When this threshold was used; the sensitivity, specificity, PPV and NPV were found as 83.8%, 83.6%, 83.8% and 83.6%, respectively. When the mean of the two measurements were taken, the threshold value in distinguishing between benign and malignant masses was found to be 4.52. This threshold value resulted in the sensitivity, specificity, PPV, NPV, and accuracy rates of 85.5%, 84.8%, 85.5%, 84.8%



**Figure 5.** ROC curve for the first threshold value of 4.6 (AUC, 0.908;  $p<0.001$ ) (blue). ROC curve for the second measurement threshold value of 4.65 (AUC, 0.918;  $p<0.001$ ) (red). ROC curve for two measurement's mean threshold value of 4.52 (AUC, 0.926;  $p<0.001$ ) (black). Significant differences were not seen between the AUC values of the measurement methods

and 85.2%, respectively. When the ROC curves for these three values were considered together, the curves were found to be similar (Figure 5).

The  $\kappa$  value for the two strain ratio measurements was 0.82, which showed an almost perfect agreement between the two strain ratio measurements in the distinction between benign and malignant lesions. The concordance correlation coefficient between the two measurements was determined as 0.87, with an almost perfect agreement (Figure 6).

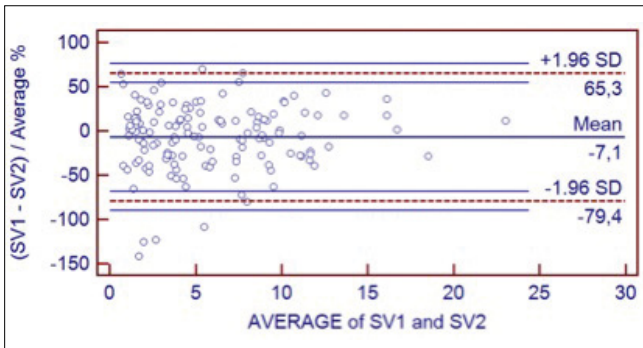
The diagnostic accuracy rate of sonoelastography in predicting malignancy was found to be higher when evaluated according to BI-RADS categories. Although strain ratio and elasticity scoring with five categories showed similar accuracy rates, the strain ratio values were found to have a higher sensitivity (Table 5).

When the mean strain ratio values were determined, 10 false positive and 10 false negative results were detected. Six of the false positive results were detected in patients with fibroadenoma, 2 in fibrotic breast tissue, 1 in fibrocystic change and 1 in fat necrosis. Seven of the false-negative results were detected in patients with invasive ductal carcinoma, one in malignant phyllodes tumor, one in granulocytic sarcoma, and one in mucinous carcinoma.

Table 5. Comparison of conventional ultrasound and sonoelastography values

| Test                             | Sensitivity (%) | Specificity (%) | PPD (%) | NPD (%) | Accuracy (%) |
|----------------------------------|-----------------|-----------------|---------|---------|--------------|
| BI-RADS (for category 4-5)       | 98.5            | 56.2            | 71.1    | 97.2    | 77.7         |
| Elasticity Score (for score 4-5) | 80.0            | 90.8            | 90.3    | 80.8    | 85.2         |
| Mean strain ratio                | 85.5            | 84.8            | 85.5    | 84.8    | 85.2         |

BIRADS: Breast imaging, report and data systems; PPD: Positive predictive value; NPD: negative predictive value



**Figure 6.** Bland-Altman: Concordance between the two measurements. There seems to be a substantial agreement between the two measurements except for a few cases

## Discussion and Conclusions

The first and the most appropriate imaging method to assess the breast in women with breast-related symptoms is mammography (11). Ultrasound is the most commonly used method to complement mammography, malignancy can be detected with high sensitivity. However, the low specificity of this method is a significant problem. Thus, a biopsy is performed for lesions that cannot be differentiated between benign or malignant in order to obtain a histopathologic diagnosis. 50- 60% of biopsied lesions are diagnosed as benign, leading to unnecessary disruption of patient comfort, anxiety and financial loss (12). Although MRI is a valuable method used in breast imaging, it is an expensive method for screening with low specificity (13, 14). Studies on a new ultrasound technique, sonoelastography, have been done in recent years in order to differentiate benign and malignant lesions of the breast in a non-invasive manner with higher sensitivity and specificity. The firmness of tissues can be displayed in real time with different color codes by sonoelastography, and a qualitative visual scoring can be performed. In qualitative sonoelastography, the elastography is shown in B-mode sonography with a color range between green (soft tissue) and blue (hard tissue). In addition, a strain ratio is calculated by using the obtained elasticity map, by dividing the strain value of the normal tissue to that of the lesion, thereby allowing a semiquantitative measure of the lesion's stiffness (15-17).

Many studies reported a higher specificity in sonoelastography in contrast to a higher sensitivity in conventional ultrasound. In the study of 281 lesions in 267 patients, Sohn et al. (18) used the six-category malignancy scoring in order to evaluate the sensitivity and specificity of conventional ultrasound. They determined the sensitivity of conventional ultrasound as 98.2% and the specificity as 44.1%, while if conventional ultrasound and sonoelastography were used in conjunction the sensitivity was determined as 89.1% and the specificity as 50.5%.

This result suggested that the sonoelastography scoring system is a method that increased the specificity of conventional ultrasound (18).

In their study with 100 lesions in 100 patients, Cho et al. (19) detected the sensitivity as 100% and specificity as 33% with a cut-off value between conventional ultrasound BI-RADS categorization category 3 and category 4a. In contrast, when the cut-off value for sonoelastography score of 2 and scored 3 were used, they determined the sensitivity as 82% and specificity as 84%.

In their study with 111 lesions in 111 patients, Itoh et al. (9) reported the sensitivity as 96.2% and specificity as 62.7%, with a cut-off value between conventional ultrasound BI-RADS categorization category 3 and category 4, while the sensitivity was 71.2%, and specificity was 96.6% with a cut-off value of BI-RADS category 4 and category 5. In contrast, when the cut-off value between sonoelastography scores 3 and 4 were used, they determined the sensitivity as 86.5% and specificity as 89.8% (9).

Okar Atabey et al. (20) evaluated 96 patients with 110 lesions by US elastography and used the 5 score system. For US elastography, the specificity was reported as 83%, sensitivity 89%, positive predictive value 79% and negative predictive value 91%.

In our study, when the threshold value for conventional ultrasound was accepted as BI-RADS 3 to 4, the sensitivity was found to be 98.5% and the specificity 56.2%. For sonoelastography, the selected threshold value was score 3, yielding a sensitivity of 80.0% and specificity of 90.8%. According to these values, in accordance with the literature, the sensitivity of conventional ultrasound was higher than that of sonoelastography, while the specificity of sonoelastography was higher as compared to US. However, selecting different threshold values changes sensitivity and specificity values.

Different threshold values were calculated in previous studies using strain ratio and in most of these studies, the sensitivity of strain ratio was found to be higher than the scoring system, while specificity was higher in the scoring system. Kumm et al. (21) studied 310 lesions in 288 patients according to the elastography scoring system with a threshold score between 2 and 3, and determined the sensitivity as 76% and specificity as 81%. In the same study, with a threshold of 4.5 for strain ratio, the sensitivity was reported as 79%, and specificity as 76%. Based on these values, it was concluded that the sensitivity of strain ratio was higher while specificity was higher in the scoring system (21). Parajuly et al. (22) studied 342 lesions in 325 patients according to the elastography scoring system with a threshold score between 3 and 4, they found the sensitivity as 77.7% and specificity as 96.2%. In the same study, with a threshold of 3.54 for strain ratio, the sensitivity was reported as 94.5%, and specificity as 94.3%. Stachs et al. (23) studied 224 lesions in 215

patients according to the elastography scoring system with a threshold score between 3 and 4, they found the sensitivity as 87.9% and specificity as 73.1%; while with a threshold of 2 for strain ratio, the sensitivity was reported as 90.7%, and specificity as 58.2%. When Yağtu et al. (24) evaluated 76 lesions of 76 patients, with a cut-off value of 4.0 they reported the sensitivity as 83.3%, specificity 76.9%, positive predictive value 62.3%, and negative predictive value as 90.7%. When the strain pattern cut-off was accepted as score 4 and 5, the sensitivity was 42.7%, specificity 94.2%, positive predictive value 77.2%, and negative predictive value was 78%. If conventional ultrasound findings were assessed in combination with elastographic strain ratio, the sensitivity was 87.5%, specificity 71.1%, positive predictive value 58.3%, and negative predictive value was 92.5% (24).

Various studies in the literature detected a threshold between 2 and 4.5. In a study on 201 lesions in 201 patients, Fischer et al. (25) adopted the strain ratio threshold as 2.27. Yerli et al. (16) evaluated 71 patients with 78 lesions, and the strain ratio threshold used in that study was 3.52. In our study, when the threshold value of 4.52 was used for sonoelastography strain ratio measurements, the sensitivity was 85.5%, specificity 84.8%, positive predictive value 85.5%, negative predictive value 84.8% and the accuracy rate was 85.2%. According to these values, similar to the literature, the specificity of sonoelastography scoring system was higher than that of the strain ratio, while the sensitivity of strain ratio was found to be higher than that of the scoring system.

In the study on interobserver compliance by Yoon et al. (26), 53 patients with 65 lesions were evaluated. The compliance according to elasticity score was reported as  $\kappa=0$ , 46, and it was shown to increase to  $\kappa = 0.79$  when the strain ratio and elasticity score were evaluated in combination (26). In our study, interobserver assessment was not performed but intraobserver agreement of measurements performed by the same person was assessed. The  $\kappa$  value was detected as 0.82 revealing an almost perfect agreement.

Ten false negative results were detected in our study. The strain ratio of the six invasive ductal carcinomas with false negative results was equal to or greater than 3.5. One of the false-negative results was a mucinous carcinoma that was previously reported to be soft in consistency (27). The size of the granulocytic sarcoma patient with a false negative result was 5 cm, and it is known that as the size increases the feasibility and accuracy of elastography decreases, additionally that lesion contained necrotic areas on pathologic examination. Two of the false positive diagnoses were pathologically diagnosed as fibrotic breast tissue, this could be due to the hardness caused by fibrosis. Similarly, the six fibroadenomas with false positive results could have been caused by the excess stromal fibrotic component of some fibroadenomas. In addition, five fibroadenoma patients with false-positive results were over 40 years of age, and the cause of false-positive results in these patients may be the presence of calcifications that cannot be displayed by ultrasound (27, 28).

The lack of diversity of malignant lesions due to the small number of lesions is a limitation of our study. In addition, lack of interobserver evaluation creates another limitation.

According to our study, although the sensitivity of conventional ultrasound was higher, the specificity of sonoelastography in both the scoring system and the strain ratio were significantly higher. These

results imply that sonoelastography is a simple, noninvasive and rapid diagnostic method that can provide a diagnostic contribution to conventional ultrasound by increasing specificity. It also may help in classification of BIRADS 3 solid mass lesions as either BIRADS 2 or 4. This might in turn reduce the rate of unnecessary biopsies, reduce anxiety in patients and may contribute to lowering biopsy costs. Sonoelastography is not a method to replace conventional breast ultrasound for detecting breast cancer, but may complement conventional breast US by increasing its diagnostic power.

**Ethics Committee Approval:** Ethics committee approval was received for this study.

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

**Author Contributions:** Concept - A.V.P., A.B.; Design - A.V.P.; Supervision - A.V.P., I.K.B.; Data Collection and/or Processing - A.V.P., I.K.B.; Analysis and/ or Interpretation - A.B., A.K.P.; Literature Review - A.B., A.V.P.; Writer - A.B., A.V.P.; Critical Review - A.K.P., I.K.B.

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

**Financial Disclosure:** The authors declared that this study has received no financial support.

## References

1. Stavros AT. 2004. Breast Ultrasound, Philadelphia, USA, Lippincott Williams, Wilkins.
2. Algül A, Balci B, Seçil M, Canda T. Meme kitlelerinde kontrastlı power Doppler ve renkli Doppler US: tanısal etkinlikleri ve ayırıcı tanıya katkıları. Tani Girişim Radyol 2003; 9:199-206. (PMID: 14661490)
3. Murat A, Arslan A, Oğur E. Benign ve malign meme kitlelerinin ayırımında renkli dupleks ultrasonografinin yeri. Fırat Tıp Dergisi 2005; 10:68-71.
4. Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. Ultrason Imaging 1991; 13:111-134. (PMID: 1858217)
5. Gao L, Parker KJ, Lerner RM, Levinson SF. Imaging of the elastic properties of tissue-a review. Ultrason Med Biol 1996; 22:959-977. (PMID: 9004420)
6. Chen EJ, Adler RS, Carson PL, Jenkins WK, O'Brien WD. Ultrasound tissue displacement imaging with application to breast cancer. Ultrason Med Biol 1995; 21:1153-1162. (PMID: 8849830)
7. Gerger D, Coşkun, ZÜ, Ertürk A, Uzun Ş. Meme Kitlelerinin Değerlendirilmesinde Elastografi ve Difüzyon MRG'nin Yeri. Okmeydanı Tıp Dergisi 2013; 29:8-14. [CrossRef]
8. Krouskop TA, Wheeler TM, Kallel F, Garra BS, Hall T. Elastic moduli of breast and prostate tissues under compression. Ultrason Imaging 1998; 20:260-274. (PMID: 10197347)
9. Itoh A, Ueno E, Tohno E, Kamma H, Takahashi H, Shiina T, Yamakawa M, Matsumura T. Breast disease: Clinical application of US elastography for diagnosis. Radiology 2006; 239:341-350. (PMID: 16484352)
10. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33:159-174. (PMID: 843571)
11. Geller BM, Barlow WE, Ballard-Barbash R, Ernster VL, Yankaskas BC, Sickles EA, Carney PA, Dignan MB, Rosenberg RD, Urban N, Zheng Y, Taplin SH. Use of the American College of Radiology BI-RADS to Report on Mammographic evaluation of women with signs and symptoms of breast disease. Radiology 2002; 222:536-542. (PMID: 11818625)

12. Boba M, Koltun U, Bobek-Billewicz B, Chmielik E, B, Olejnik T. False-negative results of breast core needle biopsies – retrospective analysis of 988 biopsies. *Pol J Radiol* 2011; 76:25-29. (PMID: 22802813)
13. Altunay E, Düşünceli E. Malign meme hastalıklarında radyolojik algoritma. *Türkiye Klinikleri J Int Med Sci* 2007; 3:75-80.
14. Altuğ A. Benign meme hastalıklarında radyolojik algoritma. *Türkiye Klinikleri J Int Med Sci* 2007; 3:65-74.
15. Garra BS. Imaging and estimation of tissue elasticity by ultrasound. *Ultrasound Q* 2007; 23:255-268. (PMID: 18090836)
16. Yerli H, Yılmaz T, Kaskati T, Gulay H. Qualitative and semi-quantitative evaluations of solid breast lesions by sonoelastography. *J Ultrasound Med* 2011; 30:179-186. (PMID: 21266555)
17. Athanasiou A, Tardivon A, Tanter M, Sigal-Zafrani B, Bercoff J, Deffieux T, Gennisson JL, Fink M, Neuenschwander S. Breast lesions: quantitative elastography with supersonic shear imaging--preliminary results. *Radiology* 2010; 256:297-303. (PMID: 20505064)
18. Sohn YM, Kim MJ, Kim EK, Kwak JY, Moon HJ, Kim SJ. Sonographic elastography combined with conventional sonography: how much is it helpful for diagnostic performance? *J Ultrasound Med* 2009; 28:413-420. (PMID: 19321669)
19. Cho N, Moon WK, Park JS, Cha JH, Jang M, Seong MH. Nonpalpable breast masses: evaluation by US elastography. *Korean J Radiol* 2008; 9:111-118. (PMID: 18385557)
20. Okar Atabey A, Arıbal E, Ergelen R, Kaya H. Ultrason Elastografinin Meme Lezyonlarının Ayrıcı Tanısındaki Yeri ve Histopatolojik Korelasyon. *J Breast Health* 2014; 10:234-238. [\[CrossRef\]](#)
21. Kumm TR, Szabunio MM. Elastography for the characterization of breast lesions: initial clinical experience. *Cancer Control* 2010; 17:156-161. (PMID: 20664512)
22. Parajuly SS, Lan PY, Yun MB, Gang YZ, Hua Z. Diagnostic potential of strain ratio measurement and a 5 point scoring method for detection of breast cancer: Chinese experience. *Asian Pac J Cancer Prev* 2012; 13:1447-1452. (PMID: 22799346)
23. Stachs A, Hartmann S, Stubert J, Dieterich M, Martin A, Kundt G, Reimer T, Gerber B. Differentiating Between Malignant and Benign Breast Masses: Factors Limiting Sonoelastographic Strain ratio. *Ultraschall Med* 2013; 34:131-136. (PMID: 23108926)
24. Yağrı M, Turan E, Öztürk Turan Ç. Meme Kitlelerinin Ayrıcı Tanısında US Elastografinin Rolü ve Klasik Ultrasonografik Değerlendirmeye Katkısı. *J Breast Health* 2014; 10:141-146.
25. Fischer T, Peisker U, Fiedor S, Slowinski T, Wedemeyer P, Diekmann F, Thomas A. Significant differentiation of focal breast lesions: raw data-based calculation of strain ratio. *Ultraschall Med* 2012; 33:372-379. (PMID: 21614749)
26. Yoon JH, Kim MH, Kim EK, Moon HJ, Kwak JY, Kim MJ. Interobserver variability of ultrasound elastography: how it affects the diagnosis of breast lesions. *AJR Am J Roentgenol* 2011; 196:730-736. (PMID: 21343520)
27. Balleyguier C, Ciolovan L, Ammari S, Canale S, Sethom S, Al Rouhbane R, Vielh P, Dromain C. Breast elastography: The technical process and its applications. *Diagnostic and Interventional Imaging* 2013; 94:503-513. (PMID: 23619293)
28. Matsubayashi RN, Imanishi M, Nakagawa S, Takahashi R, Akashi M, Momosaki S, Muranaka T. Breast ultrasound elastography and magnetic resonance imaging of fibrotic changes of breast disease: correlations between elastography findings and pathologic and short Tau inversion recovery imaging results, including the enhancement ratio and apparent diffusion coefficient. *J Comput Assist Tomogr* 2015; 39:94-101. (PMID: 25299798)

# A Rare Breast Tumor: Dermatofibrosarcoma Protuberans

Tevhide Bilgen Özcan<sup>1</sup>, Ezgi Hacıhasanoğlu<sup>1</sup>, Mehmet Ali Nazlı<sup>2</sup>, Şefika Aksoy<sup>3</sup>, Cem Leblebici<sup>1</sup>, Canan Kelten Talu<sup>1</sup>

<sup>1</sup>Clinic of Pathology, İstanbul Training and Research Hospital, İstanbul, Turkey

<sup>2</sup>Clinic of Radiology, İstanbul Training and Research Hospital, İstanbul, Turkey

<sup>3</sup>Clinic of General Surgery, İstanbul Training and Research Hospital, İstanbul, Turkey

## ABSTRACT

Dermatofibrosarcoma protuberans is a slow-growing, local aggressive fibrous tumor of the subcutaneous tissue, frequently seen in the proximal extremities and the trunk. Its occurrence in the breast is very rare. Herein, we present a female who presented with a breast mass, and aim to discuss pathological features and differential diagnosis of dermatofibrosarcoma protuberans. A 44-year-old female presented to our clinic with a mass on her breast. Physical examination revealed a 8x5.5 cm mass with multilobular nodules on the skin in the lower inner quadrant of her right breast. Her mammography revealed a hyperdense, 7.5x6.5 cm, well-demarcated, lobulated mass in the right breast, which caused nodules on the lower para-areolar portion of the breast skin. There was no axillary lymphadenopathy on both clinical and radiologic examinations. A core needle biopsy had been performed prior to her referral to our center, which revealed a 'spindle cell lesion'. The patient underwent simple mastectomy. On macroscopic examination; the skin over the lesion appeared ulcerated, and there was a well-defined solid mass, which was pale white-tan on the cut surface. Microscopic examination revealed monotonous spindle cell proliferation arranged in storiform pattern within the collagenous stroma with irregular extensions into deep adipose tissue. There were no necrosis or nuclear pleomorphism. The mitotic rate was 2-3/10 HPF. Immunohistochemically tumor cells showed diffuse CD34 positivity, and S100, EMA and SMA negativity. Based on histopathological and immunohistochemical findings, the lesion was diagnosed as dermatofibrosarcoma protuberans. Local recurrence is expected in 20-50% of these cases. Its treatment requires complete surgical excision with wide margins. Distant metastases, although rare, have been reported.

**Keywords:** Dermatofibrosarcoma, skin neoplasm, breast, diagnosis, differential

## Introduction

Dermatofibrosarcoma Protuberans (DFSP) is a rare tumor of intermediate malignancy. Alteration in Thrombocyte Growth Factor  $\beta$  chain (TGF- $\beta$ ) is held responsible in its pathogenesis. It was first described by Darier and Ferrand in 1924 as a "progressive and recurrent dermatofibroma", and in 1925 it was named as DFSP by Hoffman (1, 2). Clinically it is usually seen as a small red-brown nodule localized in the dermis. As the lesion progresses, it forms swelling on the skin surface, infiltrates through subcutaneous adipose tissue, muscles and bones thus forming a multinodular, hard, fixed mass with ulcerated and hemorrhagic areas (3, 4). Recurrence has been reported in some cases despite wide local excision (3). Magnetic resonance imaging and computerized tomography are useful methods for detecting local recurrence (5). Distant metastasis of DFSP is rare. Its standard treatment is excision of the lesion with wide surgical margins. Chemotherapy and radiotherapy play a limited role. Radiotherapy is only recommended in cases with positive surgical margins (6).

## Case Presentation

A 44-year-old female patient of foreign nationality was referred to our clinic with a mass on her right breast. Her physical examination revealed a 8x5.5 cm mass showing multilobular nodules and ulceration on the skin surface in the lower inner quadrant of her right breast. Bilateral mammography revealed a hyperdense, 7.5x6.5 cm well-demarcated, lobulated mass in the right breast, which caused nodules on the lower para-areolar portion of the breast skin (Figure 1). On ultrasound, the same lesion was heterogenous and hypoechoic. Bilateral dynamic contrast-enhanced magnetic resonance imaging was performed for preoperative staging and to rule out any accompanying lesions, which showed a 7.5x6.5 cm mass in the right breast and was interpreted as malignant. There were no axillary lymphadenopathy on both clinical and radiologic examinations. A core needle biopsy had been performed prior to her referral to our center, which revealed a 'spindle cell lesion'. The patient underwent simple mastectomy. On macroscopic examination, the skin over the lesion appeared ulcerated and necrotic. There was a well-defined solid mass which was pale white-tan on the cut surface (Figure 1). Microscopic examination



**Figure 1.** Macroscopic and radiologic (bilateral mammography) images of the lesion

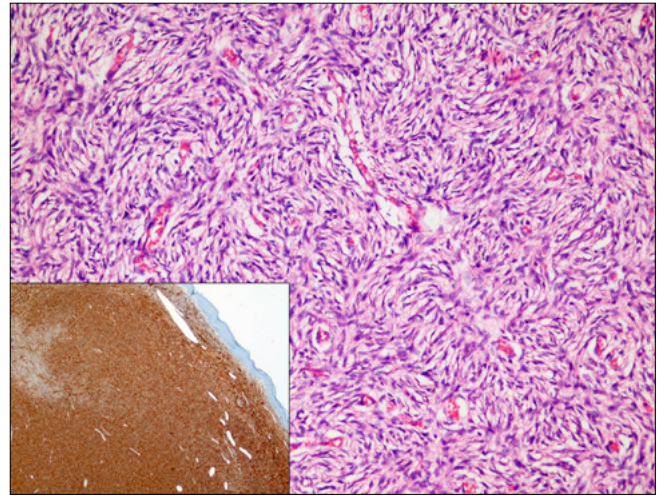
revealed monotonous spindle cell proliferation arranged in storiform pattern within the collagenous stroma (Figure 2). The lesion showed irregular extensions into deep adipose tissue (Figure 3). Necrosis and nuclear pleomorphism were not detected. The mitotic rate was 2-3/10 HPF. Immunohistochemically tumor cells showed diffuse positivity for CD34 (Figure 2-inset) and negativity for S100, EMA and SMA. Based on histopathological and immunohistochemical findings, the lesion was diagnosed as dermatofibrosarcoma protuberans. For this study, written informed consent was obtained from the patient.

### Discussion and Conclusion

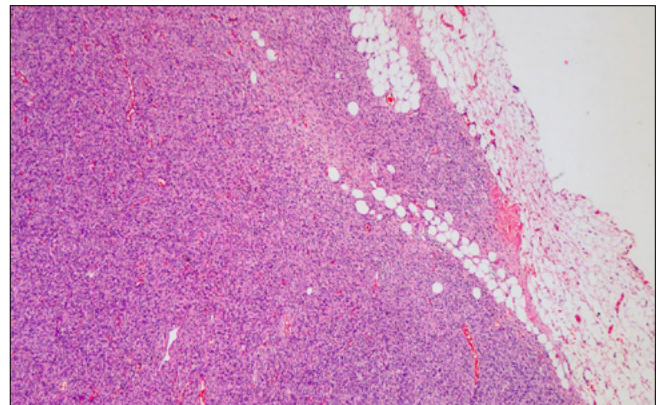
Dermatofibrosarcoma Protuberans is a local aggressive soft tissue sarcoma derived from the dermis. Local recurrence is expected in 20-50% of cases, usually within the first 3 years after excision (7-9). It can rarely metastasize by hematogenous and lymphatic route (3, 7). Brain, bone and heart metastases have been reported (8, 9). Distant metastases typically occur only after recurrences. Due to the significant role of surgical margins on local recurrence and metastasis, safe surgical margins are reported to be as wide as 4-5 cm (10, 11). In our case, simple mastectomy was performed and the distance from the tumor to the fascia was 4.5 cm. In one of the largest series in the literature, the 5-year and 10-year mortality rates were reported to be less than 2% and 3%, respectively (3). The patient is being followed-up for 9 months with no recurrence.

Microscopically, the tumor consists of uniform fibroblasts proliferation arranged in a storiform or chartwell pattern with mild nuclear pleomorphism and low mitotic activity (2-3 mitosis/10 HPF). Inflammatory cells, xanthoma cells and giant cells can rarely be detected in the tumor. The tumor can also have focal myxoid and fibrosarcomatous areas, and the local recurrence rate in such cases is reported to be high (8, 9). In our case, the tumor did not contain myxoid or fibrosarcomatous areas.

The most important entity in the differential diagnosis of DFSP is dermatofibroma. Prominent storiform pattern, increased mitotic activity and CD34 positivity in tumoral cells are not detected in dermatofibroma. Dermatofibroma is a tumor of the dermis, whereas DFSP frequently infiltrates the subcutaneous adipose tissue. Our case was distinguished from dermatofibroma with its prominent storiform pattern, increased mitotic activity (2-3/10 HPF) and diffuse positive immunohistochemical staining for CD34 (8, 9, 12). CD34, which is a myeloid progenitor cell antigen, is an important marker for the diagnosis of DFSP. It is found in endothelial cells; therefore, all vascular



**Figure 2.** Monotonous spindle cell proliferation arranged in storiform pattern within the collagenous stroma. Inset: Immunohistochemical positive staining for CD34 in tumor cells



**Figure 3.** Lesion showing extensions into the adipose tissue, low magnification view

lesions show positive staining for CD34. Its presence has also been described in many fibroblast like cells. For these reasons, CD34 is an important antigen in the differential diagnosis of DFSP (6, 8, 9, 12, 13).

Bednar tumor is known as the pigmented variant of DFSP, and it has similar morphologic properties with DFSP. The only difference is presence of melanin containing dendritic cells in the Bednar tumor. These dendritic cells show positive immunostaining for HMB-45 and S100 (8, 9, 12). Our case was immunohistochemically negative for S100.

Another important tumor in the differential diagnosis of DFSP is malignant fibrous histiocytoma (MFH). Marked nuclear pleomorphism, increased mitotic activity and necrosis are detected in MFH, and the tumor cells are negative for CD34 (5).

Our case was differentiated from leiomyoma and leiomyosarcoma by immunohistochemical positivity for CD34 and negativity for SMA, along with its morphological characteristics. These features combined with the storiform growth pattern and irregular borders of the tumor helped in distinguishing this tumor from myofibroblastoma. A spindle cell sarcoma was ruled out due to the absence of marked nuclear atypia, pleomorphism, high mitotic activity, necrosis and the presence of CD34 positivity (8, 9).

In conclusion, breast skin is a rare location for DFSP. Its definite diagnosis relies on histopathologic examination. Differential diagnosis includes various benign and malignant spindle cell lesions such as dermatofibroma, leiomyoma, myofibroblastoma, MFH and leiomyosarcoma. Diffuse positive immunohistochemical staining for CD34 is an important finding supporting the diagnosis of DFSP. Excision with wide margins is suggested due to high rates of local recurrence. Although very rare, distant metastasis can also be encountered. Clinical follow-up once in 6 months in the first 5 years, and once a year in the following 5 years is recommended in patients with DFSP (13).

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

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept- T.B.Ö.; Design - E.H.; Supervision - C.K.T.; Funding - T.B.Ö., M.A.N., Ş.A.; Materials - T.B.Ö., M.A.N., Ş.A.; Data Collection and/or Processing - T.B.Ö., E.H.; Analysis and/or Interpretation - T.B.Ö., C.L.; Literature Review - T.B.Ö., C.K.T.; Writing - T.B.Ö., E.H.; Critical Review - C.K.T., C.L.

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

**Financial Disclosure:** The authors declared that this study has received no financial support.

## References

1. Darier J, Ferrand M. Dermatofibromes progressifs et recidivants ou fibrosarcoma de la peau. *Ann Dermatol Venerol* 1924; 5:545-562.
2. Hoffmann E. Über das knollentreibende Fibrosarkom der haut (Dermatofibrosarkoma protuberans). *Dermat Ztschr* 1925; 43:1-4. [\[CrossRef\]](#)
3. Fiore M, Miceli R, Mussi C, Lo Vullo S, Mariani L, Lozza L, Collini P, Olmi P, Casali PG, Gronchi A. Dermatofibrosarcoma protuberans treated at a single institution: a surgical disease with a high cure rate. *J Clin Oncol* 2005; 23:7669-7675. (PMID: 21872132) [\[CrossRef\]](#)
4. Sin FN, Wong KW. Dermatofibrosarcomaprotuberans of the breast: a case report. *Clin Imaging* 2011; 35:398-400. [\[CrossRef\]](#)
5. Djilas-Ivanovic D, Prvulovic N, Bogdanovic-Stojanovic D, Vicko F, Sveljo O, Ivkovic-Kapic T. Dermatofibrosarcoma protuberans of the breast: mammographic, ultrasound, MRI and MRS features. *Arch Gynecol Obstet* 2009; 280:827-830. (PMID: 19252921) [\[CrossRef\]](#)
6. Llombart B, Serra-Guillén C, Monteagudo C, López Guerrero JA, Sanmartín O. Dermatofibrosarcoma protuberans: a comprehensive review and update on diagnosis and management. *Semin Diagn Pathol* 2013; 30:13-28. (PMID: 23327727) [\[CrossRef\]](#)
7. Ruiz-Tovar J, Fernández Guarino M, Reguero Callejas ME, Aguilera Velardo A, Arano Bermejo J, Cabañas Navarro L. Dermatofibrosarcoma protuberans: review of 20-years experience. *Clin Transl Oncol* 2006; 8:606-610. (PMID: 16952850) [\[CrossRef\]](#)
8. Enzinger F, Weiss S. *Soft Tissue Tumors*. Third Edition, Mosby-Year Book, Inc. St. Louis, Missouri. Chapter 14, Pages: 325-335, 1994.
9. Fletcher CD, Evans BJ, MacArtney JC, Smith N, Wilson Jones E, McKee PH. Dermatofibrosarcoma protuberans: a clinicopathological and immunohistochemical study with a review of the literature. *Histopathology* 1985; 9:921-938. (PMID: 3840767) [\[CrossRef\]](#)
10. Murphy SJ. Dermatofibrosarcoma protuberans: early recognition and treatment. *Am Fam Physician* 2000; 62:1257-1258. (PMID: 11011855)
11. Kimmel Z, Ratner D, Kim JY, Wayne JD, Rademaker AW, Alam M. Peripherical excision margins for dermatofibrosarcoma protuberans: a meta-analysis of spatial data. *Ann Surg Oncol* 2007; 14:2113-2120. (PMID: 17468914) [\[CrossRef\]](#)
12. Foroozan M, Sei JF, Amini M, Beauchet A, Saiag P. Efficacy of Mohs micrographic surgery for the treatment of dermatofibrosarcoma protuberans: systematic review. *Arch Dermatol* 2012; 148:1055-1063. (PMID: 22986859) [\[CrossRef\]](#)
13. Jiang JQ, Huang Z, Wang LH, Shen SD, Lu H. Dermatofibrosarcoma protuberans of the breast: A case report. *Oncol Lett* 2014; 8:1202-1204. (PMID: 25120687) [\[CrossRef\]](#)

# Metaplastic Breast Cancer

Halil Türkan, M. Şehsuvar Gökgöz, N. Serhat Parlak

Department of General Surgery, Uludağ University Faculty of Medicine, Bursa, Turkey

## ABSTRACT

Metaplastic Breast Cancer (MBC) is a term referring to a heterogeneous group with malignant epithelial and mesenchymal tissue components. MBC is a rare disease, accounting for 0.2% of all breast cancers. Most MBC are triple negative cancers with poor prognosis and an aggressive clinical course. Herein, we aimed to present a 74-year-old patient with metaplastic breast cancer along with clinical, radiologic and pathologic properties.

**Keywords:** Metaplastic Breast Cancer, malignant epithelial tumor, mesenchymal tumor

## Introduction

Metaplastic Breast Cancer (MBC) constitutes 0.2% of all breast cancers and was first described in 1974 by Huvos et al (1). It is usually seen in women over the age of 50 and they usually present with a large tumor size. There are no specific radiologic findings. Wargotz et al. (2) grouped MBC into five classes:

1. Carcinosarcoma,
2. Matrix-producing carcinoma,
3. Spindle-cell carcinoma,
4. Squamous cell carcinoma,
5. Osteoclastic giant cell carcinoma

Metaplastic Breast Cancer has been re-classified by the World Health Organization (WHO) in 2012 into seven groups. The detailed classification is presented in the following section of our article (Table 1). In the literature, they are reported to have a more aggressive course and worse prognosis as compared to ductal carcinoma (3).

## Case Presentation

A 74-year-old female patient was referred to our breast surgery unit due to a lump on her right breast that has been noticed 2 months ago and has been rapidly growing since then. There was no family history of breast cancer. On physical examination, there was a 10 cm lobulated mass in the right breast extending from approximately 2 cm superior to the nipple to the upper quadrants, accompanied by necrosis and ulceration of the overlying skin (Figure 1).

Mammography revealed an oval, 81x62 mm in size, regular bordered mass in the right breast upper-middle segment. In addition, a second irregular bordered, 35x32 mm in size mass was superposed over this lesion (Figure 2). Ultrasound imaging showed an irregular bordered hypochoic lesion, 22x25 mm in size, 3 cm away from the nipple at 12 o'clock position of her right breast.

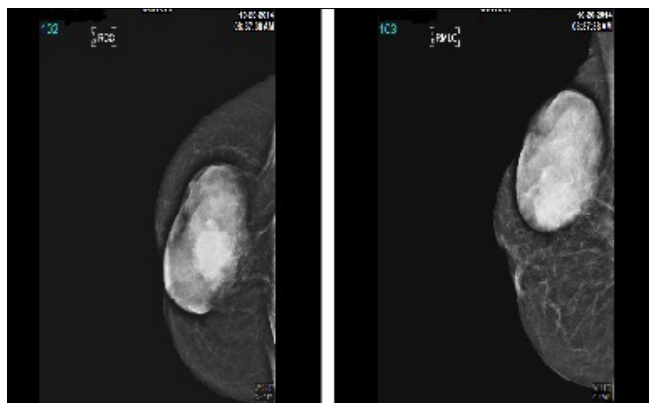
Ultrasound guided tru-cut biopsy of the lesion was performed, which revealed metaplastic carcinoma (with squamous carcinoma component). The patient who did not manifest any distant metastases underwent modified radical mastectomy.

The macroscopic evaluation displayed a 16.5x11 cm in diameter mastectomy specimen with skin ellipse that is 18x12x4.5 cm in size, and a 9x8.5x4.5 cm in size, gray-yellow-white on cut-surface, hard tumor with ulcerations that protrudes 2.7 cm out of the skin.

**Table 1. Metaplastic breast carcinoma WHO 2012 classification**

- 1- Low grade adenosquamous carcinoma
- 2- Fibromatous-like metaplastic carcinoma
- 3- Squamous cell carcinoma
- 4- Spindle cell carcinoma
- 5- Metaplastic carcinoma with mesenchymal differentiation
  - a) Chondroid differentiation
  - b) Osseous differentiation
  - c) Other types
- 6- Mixed type metaplastic carcinoma
- 7- Myoepithelial carcinoma

WHO: World Health Organization

**Figure 1.** Preoperative image of the breast**Figure 2.** Mammography; oval shaped, regular bordered lesion and a second superposed irregular bordered lesion

On histopathologic examination: Metaplastic carcinoma (with squamous cell carcinoma component), tumor size: 9x8, 5x4, 5 cm, GRADE: 3 (according to modified Bloom Richardson, tubule formation: 3, Pleomorphism: 3, Mitosis: 3) ER (Estrogen Receptor): 70% weak positive, PR (Progesterone Receptor): Negative, CerbB2: Negative (staining score: 1+), Ki67: 400/1000, P53: 30% positive.

E-Cadherin: Positive, CK5 / 6: Focal positive, EGFR (Epidermal Growth Factor Receptor): Weak-positive, CD31: Positive in endothelial and tumor cells.

Axillary dissection material revealed 2 metastatic lymph nodes and 24 benign reactive hyperplasia.

There were no postoperative complications. The patient received radiotherapy (RT) + hormonotherapy (HT) according to the multidisciplinary meeting decision.

The re-evaluation of all these findings; initially noticing a palpable breast lesion, which expanded into a lesion with skin ulceration and immunohistochemical CK5/6 positivity excluded skin squamous carcinoma, and led to a diagnosis of metaplastic breast cancer (with squamous component). An informed consent was obtained and the patient was notified of the case report.

## Discussion and Conclusions

Metaplastic Breast Cancer was re-classified by the WHO in 2012. It is usually detected in the 5<sup>th</sup> decades. Due to their propensity for rapid-growth, they are generally large on admission (tumor diameter 1-20 cm). A tumor size less than 4 cm is accepted as a good prognostic factor (4). Several cases originating from fibroadenoma or phyllodes cystosarcoma have been reported (5). Axillary lymph node metastasis is rare in this entity, 25-30%. Lymph node involvement is less than that of adenocarcinoma (6, 7). The risk of distant metastases is higher than that in adenocarcinoma. The lungs and bones are the most common sites for distant metastases.

Although there are no specific findings on mammography and ultrasound, radiologic findings vary depending on the components contained in the lesion. On mammography, they are usually visualized as well-defined, lobular-contoured masses. On US, they are seen as a mass with cystic components showing complex internal echogenicity. On MRI, they appear iso-hypointense compared to glandular tissue on T1-weighted, and hyperintense depending on the mucoid content and necrotic component on T2-weighted images (8).

Histopathologically they are within the group of triple negative tumors. They stain negative for HER2 and hormone receptors (ER, PR), and cerbB2 oncogene expression is low (9, 10). The p63 gene that plays a significant role in epithelial proliferation and differentiation was reported to be significantly high in metaplastic breast carcinomas.  $\alpha$ B -crystalline known as the heat-shock protein was also suggested as a marker for metaplastic breast carcinomas. The high expression of this protein in the tumor tissue indicates a poor prognosis (11).

Although it is reported that modified radical mastectomy and breast-conserving therapy both result in identical results in appropriate cases, there is an inclination for performing modified radical mastectomy due to the large tumor size and the high rate of local recurrence. The 5-year survival rate is 40%, and local recurrence rate is reported to be 35-62% in the first 2-5 years (12). For adjuvant treatment, anthracycline containing chemotherapy regimens are considered to be more effective (13). Radiotherapy has an important role in adjuvant treatment. MBC spreads by lymphatic and hematogenous routes. Hematogenous spread is more frequent especially in the sarcomatoid spectrum dominant types. In various retrospective studies, tumor size is reported to be a more important prognostic criterion than lymph node involvement, and that the type of metaplasia is not correlated with prognosis.

In conclusion, this is a rare type of tumor and in accordance with the literature, our patient presented with rapid growth and a large tumor size. They usually present with larger tumor size, less lymph node involvement, higher histologic grade and less hormone receptor positivity as compared to invasive ductal carcinoma. Sanguinetti et al. (14) indicated that tumor size has a major effect on the outcome. Its treatment should be more aggressive than invasive ductal carcinoma because of the higher rates of local recurrence and metastasis (15). The 5-year survival rate is 40%, and the prognosis is dismal.

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

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - H.T.; Design - H.T.; Supervision - H.T., M.Ş.G.; Materials; Data Collection and/or Processing - H.T.; Analysis and/or Interpretation - H.T., M.Ş.G.; Literature Review H.T., N.S.P.; Writing - H.T., N.S.P.; Critical Review - H.T., M.Ş.G.

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

**Financial Disclosure:** The authors declared that this study has received no financial support.

## References

- Huvos AG, Lucas JC, Foote FW. Metaplastic breast carcinoma: Rare form of mammary cancer. *NY State J Med* 1973; 73:1078-1082. (PMID: 4348806)
- Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast I: Matrix-producing carcinoma. *Human Pathol* 1989; 20:628-635. (PMID: 2544506) [CrossRef]
- Luini A, Aguilar M, Gatti G, Fasani R, Botteri E, Brito JA, Maisonneuve P, Vento AR, Viale G. Metaplastic carcinoma of the breast, an unusual disease with worse prognosis: the experience of the european Institute of Oncology and review of the literature. *Breast Cancer Res Treat* 2007; 101:349-353. (PMID: 17009109) [CrossRef]
- Oberman HA. Metaplastic carcinoma of the breast. A clinicopathologic study of 29 patients. *Am J Surg Pathol* 1987; 11:918-929. (PMID: 2825549) [CrossRef]
- Rosen PP (Ed). *Rosen's breast pathology*. Philadelphia; Lippincott Williams&Wilkins, 2001: p. 425-453.
- Carter MR, Hornick JL, Lester S, Fletcher CD. Spindlecell (sarcomatoid) carcinoma of the breast: a clinicopathologic and immunohistochemical analysis of 29 cases. *Am J Surg Pathol* 2006; 30:300-309. (PMID: 16538049)
- Karaman N, Yılmaz KB, Kebat T, Hüseyinova S, Özaslan C. 16 yaşında bir bayan hastada memenin metaplastik karsinomu. *J Breast Health* 2007; 1:35-37.
- Günhan-Bilgen I, Memis A, Üstün EE, Zekioglu O, Özdemir N. Metaplastic carcinoma of the breast: clinical, mammographic, and sonographic finding swith histopathologic correlation. *AJR* 2002; 178:1421-1425. [CrossRef]
- Al Sayed AD, El Weshi AN, Tulbah AM, Rahal MM, Ezzat AA. Metaplastic carcinoma of the breast clinical presentation, treatment results and prognostic factors. *Acta Oncol* 2006; 45:188-195. (PMID: 16546865) [CrossRef]
- Hennessy BT, Giordano S, Broglio K, Duan Z, Trent J, Buchholz TA, Barbiera G, Hortobagyi GN, Valero V. Biphasic metaplasti csarcomatoid carcinoma of the breast. *Ann Oncol* 2006; 17:605-613. (PMID: 16469754) [CrossRef]
- Sitterding SM, Wiseman WR, Schiller CL, Luan C, Chen F, Moyano JV, Watkin WG, Wiley EL, Cryns VL, Diaz LK. AlphaB-crystallin: A novel marker of invasiv basal-like and metaplastic breast carcinomas. *Ann Diagn Pathol* 2008; 12:33-40. (PMID: 18164413) [CrossRef]
- Rayson D, Adjei AA, Suman VJ, Wold LE, Ingle JN. Metaplastic breast cancer: prognosis and responseto systemic therapy. *Ann Oncol* 1999; 10:413-419. (PMID: 10370783) [CrossRef]
- Buzdar AU, Valero V, Theriault RL. Pathological complete response to chemotherapy is related to hormone receptor status. *San Antonio Breast Cancer Symposium* 2003; Abstr 302.
- Sanguinetti A, Lucchini R, Santoprete S, Farabi R, Fioriti L, Bistoni G,. Metaplastic carcinoma of the breast: Treatment, results and prognostic factors based on international literature. *Ann Ital Chir* 2014; 85:109-113. (PMID: 24195912)
- Pezzi CM, Patel-Parekh L, Cole K, Franko J, Klimberg VS, Bland K. Characteristics and treatment of metaplastic breast cancer: analysis of 892 cases from the National Cancer Data Base. *Ann Surg Oncol* 2007; 14: 166-173. (PMID: 17066230) [CrossRef]

# Unknown Effects of Breast Enhancer Products on Diagnostic Imaging Outcomes

Stefano Pacifici<sup>1</sup>, Miguel Angel De La Camara Egea<sup>2</sup>, Amaia Soria Ibarra<sup>3</sup>

<sup>1</sup>Ecotomografia Medica Srl, Unità Di Diagnostica Senologica, Rome, Italy

<sup>2</sup>Hospital Del Servicio Extremeño De Salud De Zafra, Servicio De Diagnóstico Por Imagen, Badajoz, Spain

<sup>3</sup>Centre Regional D'imagerie Medical, Amiens (Picardie), France

Dear Editor,

We have noticed that there is a significant offer of products on the web promising a breast enhancing effect.

Besides dietary supplements (1, 2), our attention was caught by some cosmetic products which proposedly act by capturing fat from food sources and store them in the breast (3). A major group of plant based dietary supplements that is on the market includes Pueraria Mirifica as the active ingredient (4, 5), and although there are only a few studies in the literature concerning the estrogenic activity of this plant extract including even an antitumor effect delineated in an in vitro study (6), there is no data concerning the safety and efficacy of this product except one study on the lipid profile and biochemical markers of bone turnover rates in healthy postmenopausal women (7). Moreover, despite the misleading advertisements, the active ingredient has not yet been approved by the FDA, as the lack of evidence is clearly delineated in the FDA report (8, 9).

Indeed, in the literature we have not been able to find any study on its effectiveness as well as the consequent alteration of breast pattern and, more importantly, its impact on the interpretation of diagnostic images. However, we found many comments in some women forum about cosmetic outcomes, mentioning an average one-breast size increase, as well as volume loss after stopping application, with no other appreciable effect (10).

Assuming the real effectiveness of such products, here not questioned, we believe it would be appropriate to initiate some clinical studies to assess how the unnatural accumulation of fat could change the appearance of the breast structure along with its impact on breast imaging in terms of challenges in comparative interpretation with previous studies. Regardless of the results of future studies, it is crucial to annotate the use of these products in women's medical history as well as warn them about their possible side effects.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - M.A.D.L.C.E.; Design - M.A.D.L.C.E.; Supervision - S.P.; Supervision - S.P.; Data Collection and/or Processing - M.A.D.L.C.E., S.I.A.; Analysis and/or Interpretation - M.A.D.L.C.E., S.P.; Literature Review - M.A.D.L.C.E., S.P.; Writing - S.P.; Critical Review - S.P.

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

**Financial Disclosure:** The authors declared that this study has received no financial support.

## References

1. Mier C. Breast Actives Review - Is the Product Really That Good? Get Curvy Now Available from: URL: <http://getcurvynow.com/reviews/breast-actives/breast-actives-review/>
2. Mier C. Read This Total Curve Review Before Buying! Available from: URL: Get Curvy Now Available from: URL: <http://getcurvynow.com/reviews/total-curve/total-curve-reviews/>
3. <http://en.jeannepiaubert.com>
4. <http://breastenhancementpillsworld.com/purafem-how-it-became-a-premium-choice/>
5. Mier C. Purafem – Pueraria Mirifica for Breast Enhancement Available from: URL: <http://getcurvynow.com/reviews/purafem-pueraria-mirifica-breast-enhancement/>

6. Jeon GC, Park MS, Yoon DY, Shin CH, Sin HS, Um SJ. Antitumor activity of spinasterol isolated from *Pueraria* roots. *Exp Mol Med* 2005; 37:111-120. (PMID: 15886524) [\[CrossRef\]](#)
7. Manonai J, Chittacharoen A, Udomsubpayakul U, Theppisai H, Theppisai U. Effects and safety of *Pueraria mirifica* on lipid profiles and biochemical markers of bone turnover rates in healthy postmenopausal women. *Menopause* 2008; 15:530-535. (PMID: 18202589) [\[CrossRef\]](#)
8. <http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0316-rpt0224-51-Tab-VII-Tab-41-Safety-Chivapat-vol162.pdf>
9. <http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s-0316-rpt0204-01-vol154.pdf>
10. [http://foro.enfemenino.com/forum/beaute1/\\_\\_\\_f9998\\_beaute1-Aumento-de-pecho-con-top-model-escultor-silueta-de-jeanne-piaubert.html](http://foro.enfemenino.com/forum/beaute1/___f9998_beaute1-Aumento-de-pecho-con-top-model-escultor-silueta-de-jeanne-piaubert.html)