E-ISSN 2587-0831

eurjbreasthealth.com

European Journal of Breast Health

Indexed in PubMed Central and Web of Science - ESCI

VOLUME: 18 • ISSUE: 2 • APRIL 2022

EUROPEAN JOURNAL OF BREAST HEALTH

Turkish Federation of Breast Diseases Societies

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

Société Internationale de Sénologie

Senologic International Society

Global Federation of Breast Healthcare Societies

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

galenos Publishing House

eurjbreasthealth.com

European Journal of Breast Health

Société Internacionale de Sénologie
Senologic International Society

Global Federation of Breast Healthcare Societies

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

TMHDF

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

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

European Journal of Breast Health indexed in PubMed Central, Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, Embase, EBSCO, CINAHL.

galenos Publishing House

Galenos Publishing House
Owner and Publisher
Derya Mor
Erkan Mor

Publication Coordinator
Burak Sever

Web Coordinators
Fuat Hocalar
Turgay Akpınar

Graphics Department
Ayda Alaca
Çiğdem Birinci
Gülay Saday
Gülşah Özgül

Project Coordinators
Aysel Balta
Duygu Yıldırım
Gamze Aksoy
Gülay Akın
Hatice Sever
Melike Eren
Özlem Çelik Çekil
Pınar Akpınar
Rabia Palazoğlu
Sümeyye Karadağ

Finance Coordinator
Sevinç Çakmak
Emre Kurtulmuş

Research&Development
Melisa Yiğitoğlu
Nihan Karamanlı

Digital Marketing Specialist
Ümit Topluoğlu

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey
Phone: +90 (212) 621 99 25 **Fax:** +90 (212) 621 99 27
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Online Publication Date: April 2022
E-ISSN: 2587-0831
International scientific journal published quarterly.

European Journal of Breast Health

European Journal of Breast Health

Aims and Scope

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

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

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

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

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

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

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

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

The European Journal of Breast Health indexed in PubMed Central, Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, Embase, EBSCO, CINAHL.

Submission Fee

The European Journal of Breast Health (Eur J Breast Health) has an open access to all articles published by itself and provides online free access as soon as it is published in the journal. We have published our journal for more than 15 years without any requests from you. But today, European Journal of Breast Health has had to charge you a low fee (50$) at the time of application to cover its increasing costs for services.

Open Access Policy

This journal provides immediate open and free access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

Open Access Policy is based on the rules of the Budapest Open Access Initiative (BOAI) http://www.budapestopenaccessinitiative.org/. By "open access" to peer-reviewed research literature, we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software, or use them for any other lawful purpose, without financial, legal, or technical barriers other than those inseparable from gaining access to the internet itself. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited.

All expenses of the journal are covered by the Turkish Federation of Breast Diseases Societies and the Senologic International Society (SIS). Potential advertisers should contact the Editorial Office. Advertisement images are published only upon the Editor-in-Chief's approval.

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, editors, editorial board, and/or publisher; the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

All published content is available online, free of charge at www.eurjbreasthealth.com.

OPEN ACCESS

Editor in Chief: Prof. 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@eurjbreasthealth.com

Web : www.eurjbreasthealth.com

Publisher: Galenos Yayınevi

Address: Molla Gürani Mah. Kaçamak Sok. 21/1
Fındıkzade, Fatih, Istanbul, Turkey

Phone : +90 (212) 621 99 25

E-mail : info@galenos.com.tr

Web : www.galenos.com.tr/en

European Journal of Breast Health

Instructions to Authors

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

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

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

Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

Manuscripts submitted to the European Journal of Breast Health will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions.

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to protect the patients' anonymity carefully. For photographs that may reveal the identity of the patients, signed releases of the patient or their legal representative should be enclosed.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with COPE guidelines.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors

(ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

2. Drafting the work or revising it critically for important intellectual content; AND

3. Final approval of the version to be published; AND

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

The European Journal of Breast Health requires corresponding authors to submit a signed and scanned version of the Copyright Transfer and Acknowledgement of Authorship Form (available for download through www.eurjbreasthealth.com) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

European Journal of Breast Health requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

When submitting a manuscript to the European Journal of Breast Health, authors accept to assign the copyright of their manuscript to Turkish Federation of Breast Diseases Societies. If rejected for publication, the copyright of the manuscript will be assigned back to the authors. European Journal of Breast Health requires each submission to be accompanied by a Copyright Transfer and Acknowledgement of Authorship Form (available for download at www.eurjbreasthealth.com). When using previously published content, including figures,

Instructions to Authors

tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s).

Statements or opinions expressed in the manuscripts published in European Journal of Breast Health reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

Submission Fee

The European Journal of Breast Health (Eur J Breast Health) has an open access to all articles published by itself and provides online free access as soon as it is published in the journal. We have published our journal for more than 15 years without any requests from you. But today, your journal has had to charge you a low fee (50$) at the time of application to cover its increasing costs for services.

The services provided in this context are the provision of systems for editors and authors, editorial work, provision of article designs, the establishment of indexing links, provision of other publishing services and support services.

You can take a look at the unbiased article evaluation process here. If you find a problem with the open access status of your article or licensing, you can contact editor@eurjbreasthealth.com

After your submission to the Eur J Breast Health evaluation system, the submission fees are collected from you or through your fund provider, institution or sponsor.

Eur J Breast Health regularly reviews the fees of submission fees and may change the fees for submission fees. When determining the costs for Eur J Breast Health submission fees, it decides according to the following developments.

- Quality of the journal,
- Editorial and technical processes of the journal,
- Market conditions,
- Other revenue streams associated with the journal

You can find the submission fees fee list here.

Article type	Price
Original articles	$50
Editorial comment	Free of charge
Review article (No application fee will be charged from invited authors)	$50
Case report	$50
Letter to the editor	Free of charge
Images in clinical practices	Free of charge
Current opinion	Free of charge
Systematic review	$50

When and How do I pay?

After the article is submitted to the Eur J Breast Health online evaluation system, an email regarding payment instructions will be sent to the corresponding author.

The editorial review process will be initiated after the payment has been made for the article.

There are two options to purchase the submission fee:

1- Making a remittance

The payment is needed to be made to the account number below. While purchasing the submission fee, please indicate your article manuscript title in the payment description section.

Account no/IBAN: TR49 0011 1000 0000 0098 1779 82 (TL)
TR17 0011 1000 0000 0098 5125 29 (USD)
TR73 0011 1000 0000 0098 5125 88 (EUR)

Account name: Meme Hastalıkları Dernekleri Federasyonu İktisadi İşletmesi

Branch code (QNB Finans Bank Cerrahpaşa): 1020

Swift code: FNNBTRISOPS

NOTE: All authors must pay the bank wire fee additionally. Otherwise, the deducted amount of the submission fee is requested from the author.

2- Virtual POS method (Credit card payment with 3D Secure)

The payment link will be sent to you for your purchase. You can contact us if you have further questions in this regard.

If you believe payment instructions are not in your email contact us via the email addresses **payment@eurjbreasthealth.com** and **journalpay@tmhdf.org.tr**

Refund policy:

The Eur J Breast Health will refund the overpayments of the submission fees for the same article or in case of multiple payments by the authors and financiers as free submission fees payment code to be used in the submission fees system.

Withdrawal of the article; There is no refund for articles whose editorial review has started in the Eur J Breast Health system. You can view article retraction policies here.

Returning the article to the author; The European Journal of Breast Health will refund the submission fees with a coupon code if the article is returned to the author. Using this code, authors can use the submission fees of different articles without making a new payment. You can view article return policies here.

Rejecting or accepting the article; Eur J Breast Health does not refund any submission fees for articles whose editorial process has started, and the process has been completed.

MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2019 - http://www.icmje.org/icmje-recommendations). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behaviour.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.

Instructions to Authors

eurjbreasthealth.com. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:

• Copyright Transfer and Acknowledgement of Authorship Form, and

• ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors)

during the initial submission. These forms are available for download at www.eurjbreasthealth.com.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions, and this page should include:

• The full title of the manuscript as well as a short title (running head) of no more than 50 characters,

• Name(s), affiliations, and highest academic degree(s) of the author(s),

• Grant information and detailed information on the other sources of support,

• Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,

• Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: An English abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Key Points: All submissions except letters to the editor should be accompanied by 3 to 5 "key points" which should emphasize the most noteworthy results of the study and underline the principle message that is addressed to the reader. This section should be structured as itemized to give a general overview of the article. Since "Key Points" targeting the experts and specialists of the field, each item should be written as plain and straightforward as possible.

Manuscript Types

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

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

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

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

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

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

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

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

Current Opinion: Current Opinion provides readers with a commentary of either recently published articles in the European Journal of Breast Health or some other hot topic selected articles. Authors are selected and invited by the journal for such commentaries. This type of article contains three main sections titled as Background, Present Study, and Implications. Authors are expected to describe the background of the subject/study briefly, critically discuss the present research, and provide insights for future studies.

Instructions to Authors

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	30	6	7 or tatal of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media
Current Opinion	300	No abstract	5	No tables	No media

Tables

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

Figures and Figure Legends

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

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

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

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

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

References

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

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

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

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

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

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

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

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

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

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

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

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be cancelled. If the submitting author(s)

believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author,and their publication approval is requested within 2 days of their receipt of the proof.

Editor in Chief: Prof. 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@eurjbreasthealth.com

Web : www.eurjbreasthealth.com

Publisher: Galenos Yayınevi

Address: Molla Gürani Mah. Kaçamak Sok. 21/1 Fındıkzade, Fatih, Istanbul, Turkey

Phone : +90 (212) 621 99 25

E-mail : info@galenos.com.tr

Web : www.galenos.com.tr

European Journal of Breast Health

Contents

REVIEW

ORIGINAL ARTICLES

European Journal of Breast Health

Contents

CASE REPORTS

LETTER TO THE EDITOR

Systematic Review

Eur J Breast Health 2022; 18(2): 108-126
DOI: 10.4274/ejbh.galenos.2021.2021-11-2

Lipid Intake and Breast Cancer Risk: Is There a Link? A New Focus and Meta-Analysis

Massimo Lodi[1,2,3], Amélie Kiehl[2], Fei Lin Qu[4], Victor Gabriele[2], Catherine Tomasetto[3], Carole Mathelin[1,3]

[1]Institut de Cancérologie Strasbourg Europe (ICANS), Strasbourg Cedex, France
[2]Department of Gynecology and Obstetrics, Strasbourg University Hospital, Strasbourg Cedex, France
[3]Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), CNRS UMR7104 INSERM U964, Illkirch-Graffenstaden, France
[4]Breast Cancer Unit, Ruijin Hospital, Shanghai, China

ABSTRACT

Objective: To determine if there is an association between total lipid intake, saturated fatty acid (SFA), Poly- and Mono-Unsaturated Fatty Acid (PUFA and MUFA) and cholesterol intake and breast cancer risk.

Materials and Methods: We conducted a systematic review of the literature and a meta-analysis following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We included all cohort and case-control studies published up to December 2020 with subgroup analysis according to menopausal status.

Results: We included 44 articles for analysis. There was no association between total fat, SFA, MUFA, PUFA and cholesterol intake and breast cancer in the general population and in pre-menopausal women. In postmenopausal women, high SFA consumption was associated with increased breast cancer risk in case-control studies [relative risk (RR): 1.12; confidence interval (CI) 95%: 1.03–1.21; p = 0.006 but not in cohort studies (RR: 1.01; CI 95%: 0.85–1.19; p = 0.93).

Conclusion: There was a weak association between high SFA consumption and breast cancer risk in post-menopausal women, however there was high heterogeneity for this analysis. As lipids can have different actions in the same family, studies should rather focus on specific lipid consumption.

Keywords: Breast cancer risk; cholesterol; dietary fat intake; mono-unsaturated fatty acid; saturated fatty acid

Cite this article as: Lodi M, Kiehl A, Qu FL, Gabriele V, Tomasetto C, Mathelin C. Lipid Intake and Breast Cancer Risk: Is There a Link? A New Focus and Meta-Analysis. Eur J Breast Health 2022; 18(2): 108-126

Key Points

- There was no association between total fat, saturated fatty-acids, mono and poly-unsaturated fatty acids and cholesterol intake and breast cancer incidence in the general population and in pre-menopausal women.
- There was a weak association between high saturated fatty acids consumption and breast cancer risk in post-menopausal women, but the results were heterogeneous.

Introduction

Among women, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related mortality worldwide. It was estimated that in 2020 it represented over 2.2 million new cases (24.5% of all cancers) and caused over 680,000 deaths (15.5% of cancer-related deaths) (1). To date, different risk factors have been identified, some of which are potentially modifiable. Breast cancer is more commonly associated with age, environmental, hormonal and lifestyle factors than genetic factors ones (2). As it represents a major public health issue and both incidence and mortality will increase in the next decades (1), prevention focuses on acting on modifiable risk factors. Among lifestyle-related breast cancer risk factors, some are commonly accepted, including lack of physical activity (3) and overweight and obesity (4), while others are still controversial. Of interest, diet is known to play a role in the development of various cancers, such as colon cancer (5). Yet, in breast cancer the role of diet remains uncertain (2). Assessing the role of diet on breast cancer risk is complex, as diet varies between individuals, cultures and territories. Moreover, different evaluation methods exist, such as consumption of a particular food, a particular nutrient, or a particular pattern. For instance, the Mediterranean diet, dairy product consumption and fruit and vegetables intake seem to have a positive impact on reducing

Corresponding Authors:
Carole Mathelin; c.mathelin@icans.eu
Massimo Lodi; massimo.lodi@chru-strasbourg.fr

Received: 12.11.2021
Accepted: 30.11.2021
Available Online Date: 01.04.2022

breast cancer incidence, while red meat consumption and alcohol intake seem to increase breast cancer risk (6). Similarly, organic food diet (7) and coffee consumption (8) seem to decrease breast cancer risk in postmenopausal women.

Commonly called "fats", lipids are, along with proteins and carbohydrates, one of the three major families of macronutrients. Natural dietary lipids, which are essential in the diet for normal nutrition, include cholesterols and fatty acids. A distinction is made between saturated (SFA), mono-unsaturated (MUFA) and poly-unsaturated (PUFA) fatty acids. However, industrial fatty acids, which are mainly unsaturated trans fatty acids (TFA), seem to increase the risk of breast cancer (9). The role of natural lipids in carcinogenesis, and in particular their carcinogenic impact on the breast, has been suggested (10). Several studies and meta-analyses investigated the impact of dietary lipid intake and breast cancer incidence but the results are contradictory and inconclusive (11-14).

Our goal was therefore to attempt to determine, through a meta-analysis based on an updated literature review including cohort and case-control studies, whether there is an association not only between total lipid intake and breast cancer, but also to determine the specific role of SFA, PUFA, MUFA, and dietary cholesterol on breast cancer risk. In addition, we performed a subgroup analysis on menopausal status.

Materials and Methods

Search Strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15). A search was conducted on the MEDLINE database for articles published up to December 2020 and written in English, French or Spanish. The query included the following keywords: "fat intake", "fatty acid", "cholesterol", "breast cancer risk", "breast carcinoma", "breast neoplasm". The full query was: ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields] OR ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "neoplasm"[All Fields]) OR "breast neoplasm"[All Fields]) OR ("breast"[All Fields] AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("risk"[MeSH Terms] OR "risk"[All Fields]))) AND ("fatty acids"[MeSH Terms] OR ("fatty"[All Fields] AND "acids"[All Fields]) OR "fatty acids"[All Fields] OR ("fatty"[All Fields] AND "acid"[All Fields]) OR "fatty acid"[All Fields] OR ("fat"[All Fields] AND ("intake"[All Fields] OR "intake s"[All Fields] OR "intakes"[All Fields])) OR ("cholesterol"[MeSH Terms] OR "cholesterol"[All Fields] OR "cholesterol s"[All Fields] OR "cholesterol"[All Fields] OR "cholesterols"[All Fields])).

Eligibility Criteria

Prospective cohort or case-control studies were included if they met the following eligibility criteria:

- Population: pre- or post-menopausal women
- Exposure: high dietary intake of total fat, SFA, MUFA, PUFA, or cholesterol
- Comparator: low dietary intake of total fat, SFA, MUFA, PUFA, or cholesterol
- Outcome: risk increase of breast cancer

In addition, we included only articles where the population of each group was provided or could be precisely calculated. If more than one study involved the same population, only the most recent study or the one with the highest number of cases was included in the analysis.

Bibliographic Selection

The initial query gave 7,088 results. These articles were analyzed by two independent reviewers (M.L. and A.K.). Based on the title and abstract, 6,761 articles were excluded because they were not directly related to the subject under study, because of an unassessed association between breast cancer and dietary lipid intake, or because they were meta-analyses, correspondence, literature reviews, basic research articles, animal or *in vitro* studies. We retained 323 articles that were selected for full-text review. Among those, a further 279 articles were excluded because they did not investigate dietary intake of total fat, SFA, MUFA, PUFA or cholesterol and breast cancer risk, because no data was available in the published paper or because it was related to the same cohort of another included article. The final selection included 44 articles for the meta-analysis. Discrepancies between the two reviewers were resolved by consensus. The bibliographic selection, with exclusion reasons, is reported in the flow chart (Figure 1).

Data Collection

For each article, one reviewer (AK) extracted the following information: first author name, year of publication, type of study (cohort or case-control), population studied (pre- or post-menopausal or both), the type of lipid (total fat, SFA, MUFA, PUFA, cholesterol) and the number of patients in each group (high versus low exposure, case and controls). In addition, country, years of inclusion, group constitution method (*i.e.*, in two groups, in tertiles, quartiles, or quintiles), principal results and adjusting variables were retrieved. Verification of all these data was performed by the second reviewer (ML).

Statistical Analysis

For each article, we compared the group with the highest intake *versus* the group with the lowest. For instance, if patients were divided into five groups (quintiles), we compared the first with the fifth. The meta-analysis was performed using R (version: 3.6.1, 2019-07-05) (16) and with the metafor package (https://metafor-project.org/). Given the heterogeneity of the populations in the different studies, the random effect model was used in the meta-analysis. The articles were weighted on the standard error of each population, which in turn depended not only on the size of the cohort but also on its homogeneity. Summary relative risk (RR) was calculated with an estimated 95% confidence interval. Heterogeneity was quantified with a maximum-likelihood estimator for Tau^2 and we calculated the Higgins' I^2 statistic. For the test of heterogeneity, the Cochran Q p-value was obtained with Wald-type test.

Results

Forty-four articles were included in the meta-analysis, consisting of 28 case-control studies (17-44) and 16 cohort studies (45-60). Results of

each study are reported in Tables 1 and 2. In total, this meta-analysis involved 1,185,896 women, of whom 54,553 had breast cancer. Table 3 summarizes the pooled analysis results according to the studied population, lipids, and study type.

Total Fat Intake

Total fat intake was evaluated in 27 case-control studies (96%) (17-41, 43, 44) and in 15 cohort studies (94%) (45-57, 59, 60). Ten studies (18, 19, 21, 36, 38, 39, 41, 43, 54, 57) found an increased risk of breast cancer with elevated total fat intake. Considering menopausal status, one study in pre-menopausal (21) and two in post-menopausal (39, 54) women found an increased risk of breast cancer. Conversely, two studies found a decreased risk with high fat intake diet (26, 44), and one of them among pre-menopausal women (44). The remaining studies did not find significant association between total fat intake and breast cancer.

In the pooled analysis, there was no significant risk increase in high total fat intake on breast cancer risk, neither for cohort [RR: 0.98; confidence interval (CI) 95%: 0.65–1.48; p = 0.93] nor case-control (RR: 1.07; CI 95% 0.96–1.19; p = 0.225) studies.

Considering menopausal status, no difference was found in pre-menopausal (RR: 1.0; CI 95%: 0.90–1.11; p = 0.98) women. In post-menopausal women both cohort and case-control pooled analysis were not significant giving relative risk results of RR: 0.94; CI 95%: 0.84 - 1.04; p = 0.24 and RR: 1.07; CI 95%: 0.94–1.21; p = 0.31, respectively.

Saturated Fatty Acids Consumption

SFA intake was evaluated in 20 case-control studies (71%) (20-22, 24-28, 30-35, 37-41, 44) and in 15 cohort studies (94%) (45-57, 59, 60). Seven studies (21, 34, 37, 41, 54, 57, 60) found an increased risk of breast cancer with elevated SFA consumption. Only one study found significant association in post-menopausal women (21). Conversely, one cohort study found a decreased risk with high SFA consumption, independently from menopausal status (45). The remaining studies did not find significant association between total fat intake and breast cancer.

In pooled analysis, there was no significant risk increase with high SFA consumption in breast cancer risk, whether it was for cohort (RR: 0.94; CI 95%: 0.74–1.18; p = 0.58) or case-control (RR: 1.06; CI 95%: 0.97: 1.17; p = 0.20) studies.

Concerning post-menopausal women (Figure 2), the pooled analysis case-control studies showed a significant increase in breast cancer risk (RR: 1.12; CI 95%: 1.03–1.21; p = 0.006) while it was not significant in cohort studies (RR: 1.01; CI 95%: 0.85–1.19; p = 0.93). No statistical difference was found in pre-menopausal women (RR: 1.02; CI 95%: 0.86–1.2; p = 0.84).

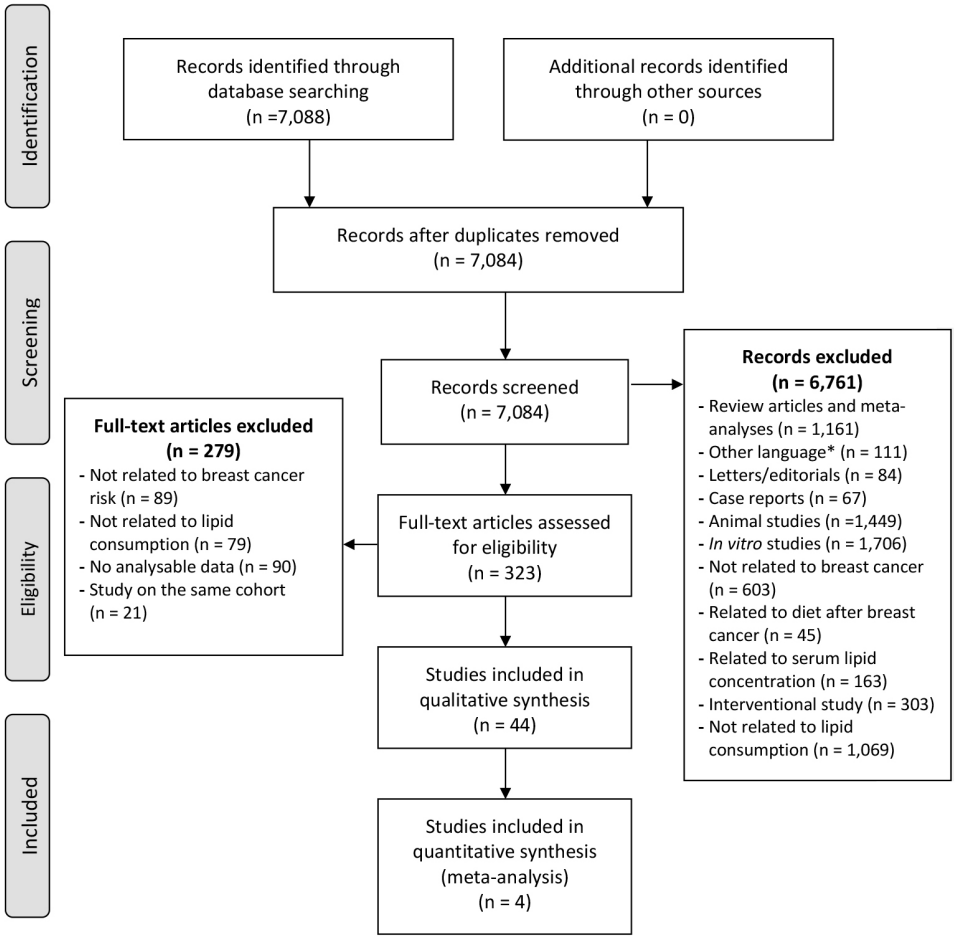

Figure 1. Flow chart diagram

n: number

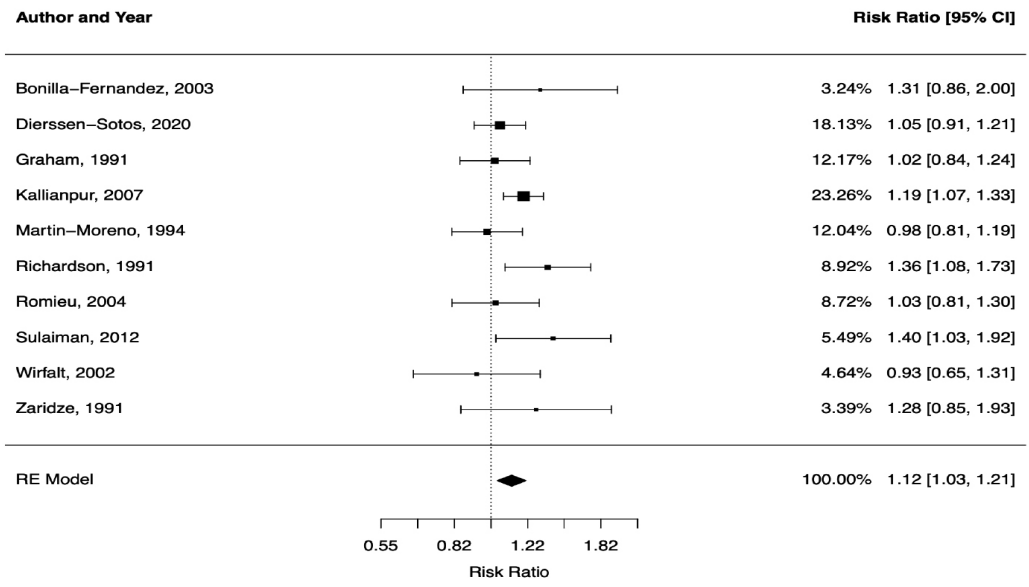

Figure 2. Forest plot of saturated fatty acids intake in case-control studies on post-menopausal women

CI: confidence interval

Unsaturated Fatty Acids Consumption

MUFA and PUFA consumption was evaluated in 15 case-control studies (54%) (21, 22, 24, 26, 28, 30, 31, 33-35, 37, 39, 40, 42, 44) and in 13 cohort studies (81%) (46-48, 50-57, 59, 60). Concerning PUFA, six articles found a decreased risk of breast cancer in women with elevated PUFA consumption (21, 22, 26, 31, 35, 40), among them one in pre-menopausal (40), and three in post-menopausal women (22, 31, 35). Conversely, five articles found an increased risk of breast cancer in women with elevated PUFA consumption (30, 34, 42, 47, 54), among them three in post-menopausal women (30, 47, 54). Concerning MUFA, six articles found an increased risk of breast cancer in women with elevated MUFA consumption (21, 30, 37, 54, 55, 57), among them four in post-menopausal women (30, 37, 54, 55). Conversely, one article found a decreased risk of breast cancer in pre-menopausal women with elevated MUFA consumption (44). The remaining studies did not find significant association between MUFA or PUFA consumption and breast cancer.

In pooled analysis there was no significant increased risk in high PUFA consumption on breast cancer risk, whether it was for cohort (RR: 1.02; CI 95%: 0.91–1.14; p = 0.78) or case-control (RR: 0.94; CI 95%: 0.82–1.08; p = 0.38) studies.

Considering menopausal status, no difference was found in pre-menopausal (RR: 1.07; CI 95%: 0.91–1.26; p = 0.42) women. In post-menopausal women both cohort and case-control pooled analysis were not significant (RR: 0.96; CI 95%. 0.83–1.11; p = 0.59 and RR: 0.88; CI 95%: 0.64–1.22; p = 0.44, respectively). Concerning MUFA, high consumption was not associated with increased breast cancer risk, whether it was for cohort (RR: 0.97; CI 95%: 0.87–1.08; p = 0.58) or case-control studies (RR: 1.03; CI 95%: 0.9–1.18; p = 0.66). No significant association was found in either pre-menopausal (RR: 0.99; CI 95%: 0.84–1.17; p = 0.93) or post-menopausal women, in either case-control studies (RR: 0.95; CI 95%: 0.83–1.08; p = 0.41) or cohort studies (RR: 1.16; CI 95%: 0.97–1.38; p = 0.11).

Cholesterol Consumption

Cholesterol consumption was evaluated in five case-control studies (18%) (21, 22, 26, 32, 34) and six cohort studies (43%) (45, 47, 48, 56, 58, 59). Three studies (34, 56, 58) found an increased risk of breast cancer with elevated cholesterol consumption, among them one found significant association in pre-menopausal women (56). None of the included studies found a decreased risk of breast cancer associated with high cholesterol consumption. The remaining studies did not find significant association between cholesterol consumption and breast cancer.

In pooled analysis there was no significant risk increase in high cholesterol consumption on breast cancer risk, whether it was for cohort (RR: 1.09; CI 95%: 0.71–1.61; p = 0.71) or case-control (RR: 1.22; CI 95%: 0.94–1.58; p = 0.13) studies.

Furthermore, no difference was found in post-menopausal women (RR: 0.98; CI 95%: 0.84–1.14; p = 0.772).

Discussion

The results of this meta-analysis does not demonstrate a statistically significant link between high consumption of total lipids, PUFA, MUFA and cholesterol and the occurrence of breast cancer. However, our results suggest that there is an association between SFA intake and breast cancer risk in postmenopausal women, although this was only found in case-controlled studies and not cohort studies. Nevertheless, it is necessary to underline the great heterogeneity in this meta-analysis. Lipid consumption may therefore play a role in breast health. Interestingly, another meta-analysis published in 2015 found a significant association between high SFA consumption and breast cancer risk among post-menopausal women, and the authors found this association only in case-control studies and not in cohort studies (61). These results are consistent with other previously published articles (62, 63). We investigated if high lipid consumption may act on breast tissue by the same mechanisms as obesity or if there were other underlying explanations.

Table 1. Case-control studies

First author, year	Country	Case (n)	Control (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Alothaimeen, 2004	Saudi Arabia	499	498	Quartiles	Total population	Total fat	RR 1.6 (0.92–2.95)	Age, menopausal status
						SFA	**RR 2.4 (1.36–4.34)***	
						PUFA	**RR 2.1 (1.17–3.83)***	
						Cholesterol	**RR 1.9 (1.03–3.44)***	
Balasubramaniam, 2013	India	152	152	Binary	Total population	**Total fat**	**RR 2.4 (2.14–5.8)***	Age, age of menopause, parity, age of first pregnancy, breastfeeding
						SFA	**RR 2.16 (1.03–4.52)***	
Bonilla-Fernandez, 2003	Mexico	138	141	Binary	Total population	Total fat	RR 0.91 (0.28–2.95)	Family history of breast cancer, age, age at menopause, BMI, total energy intake, age of first delivery, parity, breastfeeding
						SFA	RR 0.91 (0.31–2.69)	
						MUFA	RR 0.66 (0.21–2.13)	
						PUFA	RR 0.62 (0.28–1.39)	
		68	69		Pre-menopausal	Total fat	RR 1.76 (0.41–7.53)	
						SFA	RR 0.67 (0.17–2.7)	
						MUFA	RR 1.1 (0.24–4.97)	
						PUFA	RR 2.2 (0.71–6.83)	
		69	72		Post-menopausal	Total fat	RR 0.77 (0.16–3.65)	
						SFA	RR 1.74 (0.47–6.45)	
						MUFA	RR 0.62 (0.15–2.53)	
						PUFA	**RR 0.1 (0.02–0.39)***	
Challier, 1998	France	345	345	Quintiles	Total population	Total fat	RR 1.7 (0.77–3.76)	Parity, BMI, total energy intake
						SFA	RR 1.6 (0.8–3.28)	
De Stefani, 1998	Uruguay	365	397	Quartiles	Total population	Total fat	RR 1.53 (0.89–2.62)	Age, menopausal age, total energy intake, BMI, parity, alcohol consumption, family history of BC
						SFA	RR 0.84 (0.34–2.07)	
						MUFA	RR 1.5 (0.69–3.23)	

Table 1. continued

First author, year	Country	Case (n)	Control (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Dierssen-Sotos, 2020	Spain	1,181	1,682	Tertiles	Total population	Total fat	OR 0.89 (0.67–1.19)	Age, province of recruitment, educational level, family history of breast cancer, BMI, age at first delivery, hormonal contraceptive use, and postmeno- pausal hormone therapy, physical activity, smoking status, alcohol consumption, total energy intake, menopausal status
						SFA	OR 0.87 (0.65–1.16)	
						MUFA	OR 0.88 (0.68–1.15)	
						PUFA	OR 1.21 (0.93–1.58)	
					Pre-menopausal	**Total fat**	**OR 0.51 (0.31–0.86)***	
						SFA	OR 0.87 (0.51–1.48)	
						MUFA	**OR 0.51 (0.32–0.82)***	
						PUFA	OR 1.33 (0.82–2.17)	
					Post-menopausal	Total fat	OR 1.12 (0.78–1.61)	
						SFA	OR 0.84 (0.59–1.20)	
						MUFA	OR 1.15 (0.83–1.60)	
						PUFA	OR 1.16 (0.84–1.61)	
Do, 2003	Korea	224	250	Quartiles	Total population	Total fat	RR 1.7 (0.9–2.45)	Family history of breast cancer, age at menopause, BMI, total energy intake, age of first delivery, parity, breastfeeding
						SFA	RR 1.2 (0.58–2.41)	
						Cholesterol	RR 1.3 (0.67–1.98)	
Ewertz, 1990	Denmark	1,474	1,332	Quartiles	Total population	**Total fat**	**OR 1.5 (1.17–1.8)***	Age, place of residence
Franceschi, 1996	Italy	2,569	2,588	Quintiles	Total population	**Total fat**	**OR 0.81 (0.72–0.90)***	Parity, education level
						SFA	OR 0.95 (0.86–1.04)	
						PUFA	**OR 0.70 (0.61–0.79)***	
						Cholesterol	OR 0.91 (0.82–1.00)	
Goodstine, 2003	USA	565	554	Quartiles	Total population	Total fat	RR 1.1 (0.64–1.84)	Family history of breast cancer, age at menopause, BMI, age of first delivery, parity, breastfeeding
						SFA	RR 1 (0.59–1.58)	
						MUFA	RR 1.2 (0.7–1.95)	
						PUFA	RR 1.1 (0.68–1.64)	
Graham, 1991	USA	439	494	Quartiles	Post-menopausal	Total fat	OR 0.9 (0.63–1.38)	Family history of BC, menarch age, education level, BMI, parity, age of first pregnancy
						SFA	OR 1 (0.71–1.53)	

Table 1. continued

First author, year	Country	Case (n)	Control (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Kallianpur, 2007	China	3,452	3,474	Quartiles	Total population	Total fat	OR 1.1 (0.92–1.31)	Family history of breast cancer, age, age at menopause, BMI, total lipid intake, parity, age of first delivery, alcohol consumption, smoking status, breastfeeding
						SFA	**OR 1.2 (1.01–1.42)***	
						MUFA	**OR 1.3 (1.12–1.56)***	
						PUFA	OR 0.9 (0.79–1.1)	
		2,086	1,968		Pre-menopausal	Total fat	OR 1 (0.82–1.32)	
						SFA	OR 1.1 (0.9–1.42)	
						MUFA	OR 1.2 (0.97–1.51)	
						PUFA	OR 1 (0.79–1.25)	
		1,366	1,506		Post-menopausal	Total fat	OR 1.2 (0.9–1.57)	
						SFA	OR 1.3 (0.99–1.66)	
						MUFA	**OR 1.5 (1.15–1.94)***	
						PUFA	OR 0.9 (0.68–1.15)	
Khankari, 2015	USA	1,463	1,500	Quartiles	Total population	**PUFA**	**RR 1.25 (1.2 –1.63)***	Age, family history of BC, oral contraceptive intake, BMI, parity, age of first pregnancy, education level, total energy intake, total cholesterol intake, age of menopause, economic level, religion, breastfeeding, radiation exposure
Lee, 2005	Taiwan	250	219	Binary	Total population	**Total fat**	**RR 1.9 (1.1–3.2)***	Age, education level
Levi, 1993	Switzerland	107	318	Tertiles	Total population	Total fat	RR 1.5 (0.86–2.71)	Age, education level

Table 1. continued

First author, year	Country	Case (n)	Control (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Martin Moreno, 1994	Spain	762	988		Total population	Total fat	RR 0.98 (0.74–1.29)	Age, education, place of residence, BMI, total fat intake
						SFA	RR 1 (0.64–1.54)	
						MUFA	RR 0.85 (0.58–1.26)	
						PUFA	RR 1.34 (0.98–1.84)	
		247	356	Quartiles	Pre-menopausal	Total fat	RR 0.87 (0.53–1.42)	
						SFA	RR 0.77 (0.37–1.58)	
						MUFA	RR 0.71 (0.38–1.35)	
						PUFA	RR 1.58 (0.93–2.71)	
		515	632		Post-menopausal	Total fat	RR 1.1 (0.75–1.5)	
						SFA	RR 1.5 (0.91–2.62)	
						MUFA	RR 1 (0.6–1.57)	
						PUFA	RR 1.1 (0.73–1.59)	
Potischmann, 1998	USA	1,647	1,501	Quartiles	Pre-menopausal	Total fat	RR 0.9 (0.7–1.1)	Age, age at menopause, total energy intake, parity, education level, alcohol consumption
Pryor, 1989	USA	172	190	Quartiles	Pre-menopausal	Total fat	RR 0.7 (0.2–2.1)	Age, âde de menarche, BMI, Age de première grossesse, apport total en energie
		107	114	Quartiles	Post-menopausal	Total fat	RR 0.7 (0.2–2.7)	Age, menarch age, BMI, age of first pregnancy, total energy intake
Richardson, 1991	France	409	515	Tertiles	Total population	**Total fat**	**RR 1.6 (1.1–2.2)***	Age, menopause
						SFA	**RR 1.9 (1.3–2.6)***	
						MUFA	**RR 1.7 (1.2–2.5)***	
						PUFA	RR 102 (0.9–1.7)	
						Cholesterol	RR 1.3 (0.9–1.9)	
		93	133		Pre-menopausal	**Total fat**	**RR 1.8 (1-3.3)***	
						SFA	RR 1.7 (0.9–3.2)	
						MUFA	RR 2 (1.1–3.7)	
		161	202		Post-menopausal	Total fat	RR 1.4 (0.9–2.2)	
						SFA	**RR 2 (1.2–3.1)***	
						MUFA	**RR 1.5 (1–2.4)***	

Table 1. continued

First author, year	Country	Case (n)	Control (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Romieu, 2004	Mexico	475	1,391	Quartiles	Total population	Total fat	RR 0.9 (0.59–1.16)	Age, total energy intake, menopausal status, parity, family history of breast cancer
						SFA	RR 1.4 (0.83–2.25)	
						MUFA	RR 1.1 (0.67–1.91)	
						PUFA	**RR 0.5 (0.31–0.72)***	
		189	692		Pre-menopausal	Total fat	RR 1 (0.61–1.74)	
						SFA	RR 1.3 (0.59–3.01)	
						MUFA	RR 0.9 (0.39–2)	
						PUFA	RR 0.7 (0.36–1.3)	
		286	742		Post-menopausal	Total fat	RR 0.7 (0.45–1.12)	
						SFA	RR 1.2 (0.6–2.2)	
						MUFA	RR 1.6 (0.77–3.15)	
						PUFA	**RR 0.4 (0.2–0.66)***	
Sulaiman, 2012	Malasyia	382	382	Quartiles	Pre-menopausal	Total fat	RR 1.2 (0.61–2.38)	Age, family history of cancer, parity, age of first pregnancy, total fat intake, age of menopause, tobacco consumption, breastfeeding
						SFA	RR 1.6 (0.8–3.26)	
						MUFA	RR 1 (0.5–1.92)	
						PUFA	RR 0.9 (0.46–1.84)	
		166	166		Post-menopausal	**Total fat**	**RR 2.2 (1.56–3.19)***	
						SFA	RR 1.9 (0.71–3.76)	
						MUFA	RR 2.1 (0.57–2.89)	
						PUFA	RR 1.3 (0.56–3.11)	
Tayyem, 2019	Jordan	200	200	Quartiles	Total population	**Total fat**	**OR 3.87 (1.53–9.77)***	Age, marital status, education, work, income, physical activity, smoking, family history, health problem, number of pregnancies, lactation, contraceptives, hormonal replacement therapy
Toniolo, 1994	USA	180	829	Quintiles	Total population	Total fat	OR 1.5 (0.89–2.48)	Family history of breast cancer, age, age of first pregnancy, parity, BMI
						SFA	OR 1.5 (0.88–2.46)	
Van't Veer, 1990	Netherlands	133	289	Quintiles	Total population	**Total fat**	**RR 3.5 (1.64–7.64)***	Age, menarch age, age of first pregnancy, BMI, total energy intake, tobacco and alcohol consumption, parity, oral contraceptive intake, family history of BC

Table 1. continued

First author, year	Country	Case (n)	Control (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Wang, 2008	USA	1,703	2,045	Quintiles	Total population	**Total fat**	**RR 1.4 (1.1-1.65)***	Family history of breast cancer, ethicity, age, age at menopause, age of first period, place of residence, total energy intake, parity, education level, alcohol consumption, total lipid consumption, breastfeeding
						SFA	RR 0.8 (0.63–1.07)	
Wirfalt, 2002	Sweden	237	673	Quintiles	Post-menopausal	Total fat	OR 1.5 (0.92–2.49)	Age, age at menopause, total energy intake, parity, education level, alcohol consumtion, parity, BMI, total energy intake
						SFA	OR 1 (0.57–1.61)	
						MUFA	**OR 2 (1.19–5.21)***	
						PUFA	**OR 3.2 (1.75–5.21)***	
Zaridze, 1991	Russia	139	139	Binary	Post-menopausal	Total fat	RR 0.5 (0.04–7)	Menarch age, education level, total energy intake
						SFA	RR 1.7 (0.24–11.7)	
						MUFA	RR 1.8 (0.19–16.7)	
						PUFA	**RR 0.14 (0.03–0.69)***	
Zhang, 2011	China	306	132	Quartiles	Pre-menopausal	Cholesterol	RR 0.5 (0.15–1.96)	Age, BMI, age of first pregnancy, family history of BC, total fat intake, income, physical activity, education level, alcohol and tobacco consumption, breastfeeding, parity, contraception, ethnicity, marital status, professional activity, parity
						Total fat	RR 0.8 (0.56–1.17)	
						SFA	RR 0.8 (0.57–1.2)	
						MUFA	RR 0.8 (0.58–1.22)	
						PUFA	RR 0.7 (0.5–1.06)	
						Total fat	RR 0.7 (0.38–1.17)	
						SFA	RR 0.5 (0.22–1.23)	
						MUFA	RR 0.6 (0.23–1.38)	
						PUFA	**RR 0.5 (0.21–0.97)***	
					Post-menopausal	Total fat	RR 1.2 (0.52–2.94)	
						SFA	RR 1.7 (0.41–7.03)	
						MUFA	RR 2.2 (0.52–9.33)	
						PUFA	RR 0.6 (0.19–2.02)	

*Significant values are shown in bold.

RR: relative risk; OR: odds ratio; MUFA: mono-unsaturated fatty acid; PUFA: poly-unsaturated fatty acid; SFA: saturated fatty acid; BMI: body mass index

Table 2. Cohort studies

First author, year	Cohort	Country (years)	Cases (n)	Total cohort (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Byrne, 2002	**NHS**	United States (1976–1992)	1,071	44,697	Quintiles	Post-menopausal	Total fat	RR 0.94 (0.77–1.15)	Age, family history of breast cancer, BMI, parity, age at first pregnancy, alcohol consumption, age at first period, age at menopause, hormonal replacement therapy, total energy intake
							SFA	RR 0.88 (0.70–1.12)	
							MUFA	RR 1.13 (0.81–1.57)	
							PUFA	RR 0.93 (0.74–1.16)	
Farvid, 2014	**NHS II**	United States (1991–2011)	2,830	88,804	Quintiles	Total population	Total fat	RR 1.07 (0.95–1.21)	Age, family history of breast cancer, oral contraceptive, BMI, physical activity, parity, age at first delivery, education level, total energy intake, age at menopause, hormonal replacement therapy, menopausal status, alcohol consumption, smoking, fiber consumption
							SFA	RR 1.11 (0.99–1.25)	
							MUFA	RR 1.13 (1–1.27)	
							PUFA	RR 0.95(0.84–1.07)	
							Cholesterol	RR 1.05(0.87–1.26)	
						Pre–menopausal	Total fat	RR 1.07 (0.91–12.6)	
							SFA	RR 1.1 (0.93–1.29)	
							MUFA	RR 1.08 (0.91–1.27)	
							PUFA	RR 0.98 (0.83–1.15)	
							Cholesterol	**RR 1.32 (1.03–1.7)***	
						Post–menopausal	Total fat	RR 1.02 (0.83–1.26)	
							SFA	RR 1.03 (0.83–1.27)	
							MUFA	RR 1.12 (0.91–1.37)	
							PUFA	RR 0.96 (0.78–1.2)	
							Cholesterol	RR 1.03 (0.75–1.42)	
Gago-Domingez, 2003	**SCS**	Singapore (1993–1998)	314	35,298	Quartile	Total population	Total fat	RR 0.94 (0.68–1.31)	Age, family history of breast cancer, age at menopause, alcohol consumption, ethnicity
							SFA	RR 1.35 (0·69–2·61)	
							MUFA	RR 1.02 (0.73–1.43)	
							PUFA	RR 1.27 (0.92–1.74)	
Howe, 1991	**CNBSS**	Canada (1980–1987)	519	56,837	Quartile	Total population	Total fat	OR 1.35 (1–1.82)	Age, family history of breast cancer, BMI, parity, age at first delivery, education level, total energy intake, fiber consumption, age at menopause, hormonal replacement therapy
							SFA	OR 1.08 (0.43–1.59)	
							MUFA	OR 1.23 (0.81–1.89)	
							PUFA	OR 1.3 (0.93–1.82)	

Table 2. continued

First author, year	Cohort	Country (years)	Cases (n)	Total cohort (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Jones, 1987	**NHANES**	United States (1070–1975)	99	5,495	Quartile	Total population	**Total fat**	**HR 0.34 (0.16–0.73)***	Age, family history of breast cancer, BMI, menopausal status, age at menopause, age of first period
							SFA	**HR 0.44 (0.23–0.86)***	
							Cholesterol	HR 0.7 (0.36–1.37)	
Kim, 2017	**SKCCR**	Korea (2002–2014)	72	5,046	Binary	Total population	**Cholesterol**	**HR 1.69 (1.01–2.82)***	Age, family history of breast cancer, oral contraceptive, BMI, physical activity, parity, education level, age of first period, age at menopause, menopausal status, alcohol consumption, smoking
						Pre–menopausal	Cholesterol	HR 1.42 (0.75–2.67)	
						Post-menopausal	Cholesterol	HR 1.97 (0.81–4.80)	
Kushi, 1992	**IWHS**	United States (1985–1989)	459	34,388	Quartile	Post-menopausal	Total fat	RR 1.16 (0.87–1.55)	Age of first period, age at menopause, age of first delivery, BMI, alcohol consumption, total energy intake
							SFA	RR 1.07 (0.68–1.68)	
							MUFA	RR 1.9 (0.7–1.7)	
							PUFA	**RR 1.49(1.01–2.02)***	
							Cholesterol	RR 1.24 (0.87–1.76)	
Löf, 2007	**SWLHC**	Sweden (1991–2004)	974	44,569	Quintiles	Total population	Total fat	HR 1.02 (0.72–1.45)	Age, family history of cancer, oral contraceptive, BMI, parity, age of first pregnancy, education level, alcohol consumption, age of first period, total fat intake
							SFA	HR 1.12 (0.69–1.81)	
							MUFA	HR 0.88 (0.53–1.46)	
							PUFA	HR 0.72 (0.52–1)	
Park, 2012	**TSS**	United States (1993–2007)	3,885	85,089	Quintiles	Post-menopausal	Total fat	HR 0.94(.085–1.0.5)	Age, family history of cancer, BMI, parity, age of first delivery, ethnicity, age at menopause, alcohol consumtion, smoking
							SFA	HR 0.93 (0.83–1.02)	
							MUFA	HR 1.01 (0.91–1.13)	
							PUFA	HR 0.97 (0.88–1.08)	
							Cholesterol	HR 1.01(0.9–1.12)	

Table 2. continued

First author, year	Cohort	Country (years)	Cases (n)	Total cohort (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Sczaniecka, 2012	**VITAL**	United States (2000–2007)	772	29,480	Quintiles	Post-menopausal	Total fat	HR 1.43 (0.95–2.14)	Age, ethnicity, BMI, family history of breast cancer, age of first pregnancy, physical activity, age of first period, hysterectomy, oral contraceptive, total energy intake, fruit consumption, alcohol consumption, age at menopause
							SFA	HR 1.47 (1.00–2.15)	
							MUFA	**HR 1.61 (1.08–2.38)***	
							PUFA	**HR 1.07 (0.76. 1.52)**	
Sellem, 2018	**NNS**	France (2009–2017)	545	44,039	Quintiles	Total population	Total fat	HR 1.43 (0.92–2.22)	Age, family history of breast cancer, education level, alcohol consumption, smoking, BMI, total energy intake, vegetables consumption, physical activity
							SFA	**HR 1.98 (1.24–3.17)***	
							MUFA	HR 1.29 (0.76–2.21)	
							PUFA	HR 0.89 (0.62–1.28)	
Sieri, 2014	**EPIC**	Europe (1992–2004)	10,062	337,327	Quintiles	Total population	**Total fat**	**HR 1.06 (1.01–1.12)***	Menopausal status, hormone replacement therapy, alcohol consumption, smoking, education level, BMI, parity
							SFA	**HR 1.05 (1.02–1.08)***	
							MUFA	**HR 1.06 (1.02–1.11)***	
							PUFA	HR 0.98 (0.95–1.01)	
Thiébaut, 2007	**AARP DHS**	United States (1995–2000)	5,301	188,736	Quintiles	Post-menopausal	**Total fat**	**HR 1.22 (1.03–1.45)***	Age, family history of breast cancer, BMI, physical activity, parity, age of first pregnancy, age at menopause, hormone replacement therapy, alcohol consumption, smoking
							SFA	**HR 1.18 (1.06–1.31)***	
							MUFA	**HR 1.12 (1.00–1.24)***	
							PUFA	**HR 1.12(1.01–1.25)***	

Table 2. continued

First author, year	Cohort	Country (years)	Cases (n)	Total cohort (n)	Group constitution	Population	Lipid	Result	Adjusting variables
Van den Brandt, 1993	**NLCS**	Netherlands (1986–1989)	471	62,573	Binary	Post-menopausal	Total fat	RR 1.08 (0.73–1.59)	Age, family history of breast cancer, BMI, oral contraceptive, age of first period, parity, age of first pregnancy, alcohol consumption, smoking, age at menopause, total energy intake
							SFA	RR 1.39 (0.94–2.06)	
							MUFA	RR 0.75 (0.50–1.12)	
							PUFA	RR 0.95 (0.64–1.40)	
							Cholesterol	RR 1.09 (0.74–1.61)	
Velie, 2000	**BCDDP**	United States (1979–1995)	996	40,022	Quintiles	Post-menopausal	Total fat	RR 1.07 (0.86–1.32)	Age, family history of breast cancer, BMI, oral contraceptive, parity, age of first pregnancy, total energy intake, age of first period, age at menopause, education level, alcohol consumption, smoking
							SFA	RR 1.12(0.87–1.45)	
Wakai, 2005	**JACC Study**	Japan (1988–1997)	129	26,991	Quintiles	Total population	Total fat	RR 0.80 (0.46–1.38)	Age, family history of breast cancer, oral contraceptive, BMI, age of first period, parity, age at first pregnancy, education level, place of residence, age at menopause
							SFA	RR 0.68 (0.40–1.15)	
							MUFA	RR 1.1 (0.63–1.9)	
							PUFA	RR 0.62 (0.36–1.09)	
						Post-menopausal	Total fat	RR 0.99 (0.5–1.95)	
							SFA	RR 0.64 (0.34–1.22)	
							MUFA	RR 0.96 (0.45–2.05)	
							PUFA	RR 1.98 (0.94–4.18)	

*Significant values are shown in bold.

RR: relative risk; HR: hazard risk; OR: odds ratio; MUFA: mono-unsaturated fatty acid; PUFA: poly-unsaturated fatty acid; SFA: saturated fatty acid; BMI: Body Mass Index; AARP DHS: American Association of Retired Persons, Diet and Health study; BCDDP: Breast Cancer Detection, Demonstration Project; CNBSS: Canadian National Breast Screening Study; EPIC: European Prospective Investigation into Cancer and Nutrition, IWHS: Iowa Women's Health Study, JACC Study: Japan Collaborative Cohort Study, NHANES: National Health and Nutrition Examination Survey; NHS Nurses' Health Study; NLCS: Netherlands Cohort Study; NNS: Nutri-Net Santé; SCS: Cancer Screenee Cohort Study; SKCCR: South Korea Central Cancer Registry; SWLHC: Scandinavian Women's Lifestyle and Health Cohort; TSS: The Sister Study; VITAL: VITamins and Lifestyle; n: number

Table 3. Meta-analysis results

Population	Lipid	Study type	Studies (n)	RR	(95% CI)	p-value	I2 (%)
Total population	Total fat	Cohort	8	0.98	(0.65–1.48)	0.9311	97
		Case-Control	20	1.07	(0.96–1.19)	0.225	89
	SFA	Cohort	8	0.94	(0.74–1.18)	0.579	92
		Case-Control	15	1.06	(0.97–1.17)	0.198	82
	MUFA	Cohort	8	0.97	(0.87–1.08)	0.578	56
		Case-Control	10	1.03	(0.9–1.18)	0.659	90
	PUFA	Cohort	8	1.02	(0.91–1.14)	0.780	64
		Case-Control	12	0.94	(0.82–1.08)	0.384	91
	Cholesterol	Cohort	3	1.09	(0.71–1.66)	0.706	69
		Case-Control	6	1.22	(0.94–1.58)	0.129	92
Pre-menopausal	Total fat	Case-Control	9	1	(0.9–1.11)	0.981	55
	SFA	Case-Control	7	1.02	(0.86–1.2)	0.838	70
	MUFA	Case-Control	7	0.99	(0.84–1.17)	0.931	71
	PUFA	Case-Control	6	1.07	(0.91–1.26)	0.421	67
Post-menopausal	Total fat	Cohort	8	0.94	(0.84–1.04)	0.242	62
		Case-Control	11	1.07	(0.94–1.21)	0.309	66
	SFA	Cohort	8	1.01	(0.85–1.19)	0.932	84
		Case-Control	10	**1.12**	**(1.03–1.21)**	**0.006**	**26**
	MUFA	Cohort	7	0.95	(0.83–1.08)	0.413	69
		Case-Control	9	1.16	(0.97–1.38)	0.108	82
	PUFA	Cohort	7	0.96	(0.83–1.11)	0.592	77
		Case-Control	8	0.88	(0.64–1.22)	0.444	94
	Cholesterol	Cohort	4	0.98	(0.84–1.14)	0.772	42

Significant values are shown in bold.

RR: relative risk; CI 95%: confidence internal at 95%; I2: Higgin's I2 statistic of heterogeneity; MUFA: mono-unsaturated fatty acid; PUFA: poly-unsaturated fatty acid; SFA: saturated fatty acid, n: number

Role of Obesity in Breast Carcinogenesis

Obesity, a documented breast cancer risk factor after menopause (4), is directly related to physical activity and diet (64). Mechanisms underlying the increased risk of breast cancer related to overweight and obesity are becoming better known and seem to rely largely on metabolic changes related to the endocrine action of excessive adipose tissue. These are mainly due to changes in steroid hormone metabolism as well as the action of inflammatory mediators (64). Mechanisms involving steroid hormones are the predominant hypothesis to explain the associations between obesity and breast cancer. The two main sites of estrogen synthesis are the ovaries before menopause, and adipose tissue through aromatization of adrenal androgen and ovarian androgens after menopause (65). Once released, estrogens act on breast epithelial cells and as a promoter of cell proliferation and this leads to an increased risk of mutation and malignant transformation of breast cells (65). This partly explains the increased risk of breast cancer after menopause in overweight or obese women. However, adipocytes, which are present in large numbers in breast tissue, secrete a range of adipokines/cytokines. Two of the cytokines are leptin and adiponectin. Leptin is a pro-inflammatory cytokine that causes post-prandial satiety and activation of cell proliferation. Adiponectin has an anti-inflammatory and antineoplastic action (66). These two cytokines balance each other in normal body weight, but in obese people there is a loss of this balance. and the production of pro-inflammatory cytokines is promoted. Clinical and experimental studies (67, 68), have found a deleterious link between adipocytes present at the tumor invasion front and the progression of breast cancer (69, 70). Breast adipocytes are involved in tumor initiation, proliferation, progression and metastasis (66). Adipocytes now appear to be important cellular contributors to tumor progression. Taken together, these biological mechanisms may explain how obesity increases breast cancer risk.

Lipid Consumption Is Not Directly Linked to Obesity

However, diet and obesity may not have an effect on the breast through the same mechanisms. Indeed, lipid consumption is not directly related to obesity and overweight. There is evidence that high total energy intake (71) and high carbohydrate intake (72) are directly related to weight gain. The link between obesity and higher

fat consumption without an increase in total energy consumption is still debated. Surprisingly, epidemiological studies do not demonstrate the role of high lipid intake in the occurrence of obesity, beyond their contribution to making the energy balance positive. In the European Prospective Investigation into Cancer and Nutrition (EPIC) prospective study of over 89,000 subjects with mean lipid intakes of 31.5%–36.5% of total energy intake, dietary lipids were not associated with weight change (73). In addition, weight gain appears to be independent of the percentage of total fat consumed (74) and there is no evidence that overweight subjects ingest more lipids than others (75). Therefore, there must be other biological explanations for our findings.

Specificity and Action of Different Lipid Subtypes

The role of the different classes of fatty acids in breast carcinogenesis has been the subject of numerous studies, mainly based on animal models. In these models, high lipid intake (40% of ingested energy) stimulated mammary carcinogenesis with a dose-effect, independent from the nature of the lipids that made up the diet (76).

We found that high SFA consumption may increase breast cancer risk among post-menopausal women. However, biological mechanisms linking SFA and breast cancerogenesis are still unknown. *In vitro* studies on a breast cancer cell line (MDA-MB-231) found that SFA stimulated proliferation while unsaturated fatty acids inhibited proliferation and induced apoptosis (77). Still, a possible explanation would be that SFA intake increased insulin resistance and may therefore lead to an increased breast cancer risk (78). However, results of our meta-analysis do not show a significant impact of PUFA, MUFA and cholesterol consumption on breast cancer risk. Unlike SFA, MUFA derived from olive oil reduced insulin resistance and therefore had a benefit on breast cancer risk (79). However, this was not found for non-vegetable MUFA. Results from the E3N-EPIC study found that high plasma levels of natural MUFA were not associated with an increased breast cancer risk while there was an increased risk for *trans*-mono-saturated fatty acids (9).

PUFA may reduce the binding between estrogen and serum proteins, including sex-hormone binding globulin (SHBG) and albumin, thereby increasing the circulating level of biologically potent estrogens that can activate breast cell growth (76). Long-chain PUFA such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can inhibit the production of arachidonic acid-derived eicosanoids in tumors (80). Lipid peroxidation can induce apoptosis (81, 82). The n-3 PUFA can therefore bind and activate the peroxisome proliferator-activated gamma receptor, leading to activation of the proteoglycan syndecan-1 in human breast cancer cells, thereby inducing apoptosis and inhibition of cell growth (80). Linoleic acid can generate 13-hydroxylinoleic acid, which enhances the growth-stimulating signal of peptide growth factors, such as epidermal growth factor (EGF) and insulin, which may stimulate the growth of cancer cells (83). A meta-analysis found that high plasma levels of n-3 PUFA were associated with a decreased risk of breast cancer (84). Conversely, high levels of MUFA and SFA (palmitic and oleic acids) were associated with increased breast cancer risk (84).

High blood cholesterol levels appear to increase the risk of breast cancer (85). Interventional studies in mice have highlighted the role of cholesterol in mammary tumor cells (86). Some derivatives such as 6-oxo-cholestan-3β,5α-diol (OCDO) and 27-hydroxycholesterol (27HC) are involved in the promotion, proliferation and migration of cancer cells (87, 88). To date, it is not confirmed that high dietary cholesterol intake is a risk factor for breast cancer, as shown in our meta-analysis and other articles (89, 90). This may be explained in part by the low proportion of cholesterol (about 30%) in the diet, while the rest comes from the degradation of lipids and carbohydrates by the liver (91).

Limitations of Our Study

It is important to consider certain elements that may have led to sources of bias in our results in view of the great heterogeneity of the selected studies. In fact, the studies included in our meta-analysis were carried out on populations from five continents with significant cultural and dietary diversity. The types of oils used in the diet also vary from one country to another, with a particular consumption of olive oil around the Mediterranean rim, as for example in Italy (26) or Spain (24), which is one of the main sources of MUFA. Conversely, in the United States and Canada, MUFA are largely provided by products of animal origin (46, 55). In Asian countries such as China, Korea, Japan and Singapore, women have a diet that is predominantly vegetarian or with low meat content (40, 51, 52). Moreover, each lipid family (SFA, MUFA, PUFA) contains a broad range of lipids. As previously described, effects may differ even among the same family. Consequently, it is possible that our results do not reflect the effect of a particular lipid, which may be specifically implicated in breast carcinogenesis.

In addition, methods of data collection, which differed across studies, must be considered when explaining the differences in outcomes between cohort and case-control studies. Case-control studies are subject to a recall bias, as dietary habits were collected with a questionnaire after the onset of the disease. Conversely, the results of cohort surveys are considered more conclusive because they are based on the collection of dietary habits in healthy subjects at the beginning of the studies and have a prospective setting. Moreover, cohort studies have a higher number of patients and a longer duration of follow-up (up to 20 years) and therefore higher statistical power.

Finally, our results were adjusted according to menopausal status but not with other variables, as data was not available for the meta-analysis. In the different studies, relative risks and odds ratio were adjusted with different variables such as body mass index, age, and parity. These variables are reported in Tables 1 and 2.

Conclusion

Despite the heterogeneity of the included articles, follow-up durations, populations and number of patients, most studies are consistent with respect to total lipids, MUFA, PUFA and cholesterol. Nevertheless, an association was found between high intake of SFA and the occurrence of breast cancer in post-menopausal women for case-controlled studies but not for cohort studies, requiring additional investigation. These studies should focus more on the type of SFA rather than the whole lipid family, as each lipid intake may have specific consequences.

At this stage, therefore, it is not possible to establish nutritional recommendations regarding the consumption of lipids to decrease breast cancer risk. However, even if lipid intake does not play a significant role in the etiology of breast cancer, its proven adverse effect on pathologies, such as cardiovascular disease, justifies the consolidation of nutritional education efforts.

Moreover, adipocytes have a role in promoting and regulating breast cancer. Current studies are of interest (87, 92) and contribute to an understanding of biochemical mechanisms. The discovery of new molecules with anti-tumor properties, such as dendrogenin A (DDA), a natural cholesterol derivative (87), opens doors to the development of new therapeutics.

Acknowledgements

The authors are thankful to the patient association Seins et Vie (SEVE) for the help and support.

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.L.Q., C.M.; Design: M.L., C.M.; Data Collection and/or Processing: M.L., A.K., F.L.Q.; Analysis and/or Interpretation: M.L., V.G., C.T.; Literature Search: M.L., A.K., F.L.Q.; Writing: M.L., A.K., F.L.Q., V.G., C.T., C.M.

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

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

References

1. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available at: https://gco.iarc.fr/today, accessed [24/01/2021]. 2020 [Crossref]
2. Rojas K, Stuckey A. Breast Cancer Epidemiology and Risk Factors. Clin Obstet Gynecol 2016; 59: 651-672. (PMID: 27681694) [Crossref]
3. Thune I, Brenn T, Lund E, Gaard M. Physical activity and the risk of breast cancer. N Engl J Med 1997; 336: 1269-1275. (PMID: 9113929) [Crossref]
4. Arnold M, Pandeya N, Byrnes G, Renehan PAG, Stevens GA, Ezzati PM, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol 2015; 16: 36-46. (PMID: 25467404) [Crossref]
5. Howe GR, Aronson KJ, Benito E, Castelleto R, Cornée J, Duffy S, et al. The relationship between dietary fat intake and risk of colorectal cancer: evidence from the combined analysis of 13 case-control studies. Cancer Causes Control 1997; 8: 215-228. (PMID: 9134246) [Crossref]
6. De Cicco P, Catani MV, Gasperi V, Sibilano M, Quaglietta M, Savini I. Nutrition and Breast Cancer: A Literature Review on Prevention, Treatment and Recurrence. Nutrients 2019; 11: 1514. (PMID: 31277273) [Crossref]
7. Baudry J, Assmann KE, Touvier M, Allès B, Seconda L, Latino-Martel P, et al. Association of Frequency of Organic Food Consumption With Cancer Risk: Findings From the NutriNet-Santé Prospective Cohort Study. JAMA Intern Med 2018; 178: 1597-1606. (PMID: 30422212) [Crossref]
8. Nehlig A, Reix N, Arbogast P, Mathelin C. Coffee consumption and breast cancer risk: a narrative review in the general population and in different subtypes of breast cancer. Eur J Nutr 2021; 60: 1197-1235. (PMID: 33442757) [Crossref]
9. Chajès V, Thiébaut AC, Rotival M, Gauthier E, Maillard V, Boutron-Ruault MC, et al. Association between serum trans-monounsaturated fatty acids and breast cancer risk in the E3N-EPIC Study. Am J Epidemiol 2008; 167: 1312-1320. (PMID: 18390841) [Crossref]
10. Cowen S, McLaughlin SL, Hobbs G, Coad J, Martin KH, Olfert IM, et al. High-Fat, High-Calorie Diet Enhances Mammary Carcinogenesis and Local Inflammation in MMTV-PyMT Mouse Model of Breast Cancer. Cancers (Basel) 2015; 7: 1125-1142. (PMID: 26132316) [Crossref]
11. Cao Y, Hou L, Wang W. Dietary total fat and fatty acids intake, serum fatty acids and risk of breast cancer: A meta-analysis of prospective cohort studies. Int J Cancer 2016; 138: 1894-1904. (PMID: 26595162) [Crossref]
12. Hunter DJ, Spiegelman D, Adami HO, Beeson L, van den Brandt PA, Folsom AR, et al. Cohort studies of fat intake and the risk of breast cancer--a pooled analysis. N Engl J Med 1996; 334: 356-361. (PMID: 8538706) [Crossref]
13. Boyd NF, Martin LJ, Noffel M, Lockwood GA, Trichler DL. A meta-analysis of studies of dietary fat and breast cancer risk. Br J Cancer 1993; 68: 627-636. (PMID: 8353053) [Crossref]
14. Dandamudi A, Tommie J, Nommsen-Rivers L, Couch S. Dietary Patterns and Breast Cancer Risk: A Systematic Review. Anticancer Res 2018; 38: 3209-3222. (PMID: 7927867) [Crossref]
15. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336-431. (PMID: 19621072) [Crossref]
16. R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing; 2019. (http://lib.stat.cmu.edu/R/CRAN/doc/manuals/r-devel/fullrefman.pdf [Crossref]
17. Pryor M, Slattery ML, Robison LM, Egger M. Adolescent diet and breast cancer in Utah. Cancer Res 1989; 49: 2161-2167. (PMID: 2539254) [Crossref]
18. Ewertz M, Gill C. Dietary factors and breast-cancer risk in Denmark. Int J Cancer 1990; 46: 779-784. (PMID: 2228305) [Crossref]
19. Van't Veer P, Kok FJ, Brants HA, Ockhuizen T, Sturmans F, Hermus RJ. Dietary fat and the risk of breast cancer. Int J Epidemiol 1990; 19: 12-18. (PMID: 2351506) [Crossref]
20. Graham S, Hellmann R, Marshall J, Freudenheim J, Vena J, Swanson M, et al. Nutritional epidemiology of postmenopausal breast cancer in western New York. Am J Epidemiol 1991; 134: 552-566. (PMID: 1951261) [Crossref]
21. Richardson S, Gerber M, Cenee S. The role of fat, animal protein and some vitamin consumption in breast cancer: a case control study in southern France. Int J Cancer 1991; 48: 1-9. (PMID: 2019449) [Crossref]
22. Zaridze D, Lifanova Y, Maximovitch D, Day NE, Duffy SW. Diet, alcohol consumption and reproductive factors in a case-control study of breast cancer in Moscow. Int J Cancer 1991; 48 : 493-501. (PMID: 2045197) [Crossref]
23. Levi F, La Vecchia C, Gulie C, Negri E. Dietary factors and breast cancer risk in Vaud, Switzerland. Nutr Cancer 1993; 19: 327-335. (PMID: 8346081) [Crossref]
24. Martin-Moreno JM, Willett WC, Gorgojo L, Banegas JR, Rodriguez-Artalejo F, Fernandez-Rodriguez JC, et al. Dietary fat, olive oil intake and breast cancer risk. Int J Cancer 1994; 58: 774-780. (PMID: 7927867) [Crossref]
25. Toniolo P, Riboli E, Shore RE, Pasternack BS. Consumption of meat, animal products, protein, and fat and risk of breast cancer: a prospective cohort study in New York. Epidemiology 1994; 5: 391-397. (PMID: 7918807) [Crossref]
26. Franceschi S, Favero A, Decarli A, Negri E, La Vecchia C, Ferraroni M, et al. Intake of macronutrients and risk of breast cancer. Lancet 1996; 347: 1351-1356. (PMID: 8637339) [Crossref]
27. Challier B, Perarnau JM, Viel JF. Garlic, onion and cereal fibre as protective factors for breast cancer: a French case-control study. Eur J Epidemiol 1998; 14: 737-747. (PMID: 9928867) [Crossref]

28. De Stefani E, Deneo-Pellegrini H, Mendilaharsu M, Ronco A. Essential fatty acids and breast cancer: a case-control study in Uruguay. Int J Cancer 1998; 76: 491-494. (PMID: 9590123) [Crossref]
29. Potischman N, Weiss HA, Swanson CA, Coates RJ, Gammon MD, Malone KE, et al. Diet during adolescence and risk of breast cancer among young women. J Natl Cancer Inst 1998; 90: 226-233. (PMID: 9462680) [Crossref]
30. Wirfält E, Mattisson I, Gullberg B, Johansson U, Olsson H, Berglund G. Postmenopausal breast cancer is associated with high intakes of omega6 fatty acids (Sweden). Cancer Causes Control 2002; 13: 883-893. (PMID: 12588084) [Crossref]
31. Bonilla-Fernández P, López-Cervantes M, Torres-Sánchez LE, Tortolero-Luna G, López-Carrillo L. Nutritional factors and breast cancer in Mexico. Nutr Cancer 2003; 45: 148-155. (PMID: 12881007) [Crossref]
32. Do MH, Lee SS, Jung PJ, Lee MH. Intake of dietary fat and vitamin in relation to breast cancer risk in Korean women: a case-control study. J Korean Med Sci 2003; 18: 534-540. (PMID: 12923330) [Crossref]
33. Goodstine SL, Zheng T, Holford TR, Ward BA, Carter D, Owens PH, et al. Dietary (n-3)/(n-6) fatty acid ratio: possible relationship to premenopausal but not postmenopausal breast cancer risk in U.S. women. J Nutr 2003; 133: 1409-1414. (PMID: 12730430) [Crossref]
34. Alothaimeen A, Ezzat A, Mohamed G, Muammar T, Al-Madouj A. Dietary fat and breast cancer in Saudi Arabia: a case-control study. East Mediterr Health J 2004; 10: 879-886. (PMID: 16335776) [Crossref]
35. Romieu I, Lazcano-Ponce E, Sanchez-Zamorano LM, Willett W, Hernandez-Avila M. Carbohydrates and the risk of breast cancer among Mexican women. Cancer Epidemiol Biomarkers Prev 2004; 13: 1283-1289. (PMID: 15298947) [Crossref]
36. Lee MM, Chang IY, Horng CF, Chang JS, Cheng SH, Huang A. Breast cancer and dietary factors in Taiwanese women. Cancer Causes Control 2005; 16: 929-937. (PMID: 16132802) [Crossref]
37. Kallianpur AR, Lee SA, Gao YT, Lu W, Zheng Y, Ruan ZX, et al. Dietary animal-derived iron and fat intake and breast cancer risk in the Shanghai Breast Cancer Study. Breast Cancer Res Treat 2008; 107: 123-132. (PMID: 17431764) [Crossref]
38. Wang J, John EM, Horn-Ross PL, Ingles SA. Dietary fat, cooking fat, and breast cancer risk in a multiethnic population. Nutr Cancer 2008; 60: 492-504. (PMID: 18584483) [Crossref]
39. Sulaiman S, Shahril MR, Shaharudin SH, Emran NA, Muhammad R, Ismail F, et al. Fat intake and its relationship with pre- and post-menopausal breast cancer risk: a case-control study in Malaysia. Asian Pac J Cancer Prev 2011; 12: 2167-2178. (PMID: 22296351) [Crossref]
40. Zhang CX, Ho SC, Lin FY, Chen YM, Cheng SZ, Fu JH. Dietary fat intake and risk of breast cancer: a case-control study in China. Eur J Cancer Prev 2011; 20: 199-206. (PMID: 21403522) [Crossref]
41. Balasubramaniam SM, Rotti SB, Vivekanandam S. Risk factors of female breast carcinoma: a case control study at Puducherry. Indian J Cancer 2013; 50: 65-70. (PMID: 23713049) [Crossref]
42. Khankari NK, Bradshaw PT, Steck SE, He K, Olshan AF, Shen J, et al. Polyunsaturated fatty acid interactions and breast cancer incidence: a population-based case-control study on Long Island, New York. Ann Epidemiol 2015; 25: 929-935. (PMID: 26452606) [Crossref]
43. Tayyem RF, Mahmoud RI, Shareef MH, Marei LS. Nutrient intake patterns and breast cancer risk among Jordanian women: a case-control study. Epidemiol Health 2019; 41: e2019010. (PMID: 30999736) [Crossref]
44. Dierssen-Sotos T, Gómez-Acebo I, Palazuelos C, Gracia-Lavedan E, Pérez-Gómez B, Oribe M, et al. Fatty acid intake and breast cancer in the Spanish multicase-control study on cancer (MCC-Spain). Eur J Nutr 2020; 59: 1171-1179. (PMID: 31069457) [Crossref]
45. Jones DY, Schatzkin A, Green SB, Block G, Brinton LA, Ziegler RG, et al. Dietary fat and breast cancer in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. J Natl Cancer Inst 1987; 79: 465-471. (PMID: 3476789) [Crossref]
46. Howe GR, Friedenreich CM, Jain M, Miller AB. A cohort study of fat intake and risk of breast cancer. J Natl Cancer Inst 1991; 83: 336-340. (PMID: 1995917) [Crossref]
47. Kushi LH, Sellers TA, Potter JD, Nelson CL, Munger RG, Kaye SA, et al. Dietary fat and postmenopausal breast cancer. J Natl Cancer Inst 1992; 84: 1092-1099. (PMID: 1619683) [Crossref]
48. van den Brandt PA, van't Veer P, Goldbohm RA, Dorant E, Volovics A, Hermus RJ, et al. A prospective cohort study on dietary fat and the risk of postmenopausal breast cancer. Cancer Res 1993; 53: 75-82. (PMID: 8416752) [Crossref]
49. Velie E, Kulldorff M, Schairer C, Block G, Albanes D, Schatzkin A. Dietary fat, fat subtypes, and breast cancer in postmenopausal women: a prospective cohort study. J Natl Cancer Inst 2000; 92: 833-839. (PMID: 10814679) [Crossref]
50. Byrne C, Rockett H, Holmes MD. Dietary fat, fat subtypes, and breast cancer risk: lack of an association among postmenopausal women with no history of benign breast disease. Cancer Epidemiol Biomarkers Prev 2002; 11: 261-265. (PMID: 11895875) [Crossref]
51. Gago-Dominguez M, Yuan JM, Sun CL, Lee HP, Yu MC. Opposing effects of dietary n-3 and n-6 fatty acids on mammary carcinogenesis: The Singapore Chinese Health Study. Br J Cancer 2003; 89: 1686-1692. (PMID: 14583770) [Crossref]
52. Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, et al. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. Cancer Sci 2005; 96: 590-599. (PMID: 16128744) [Crossref]
53. Löf M, Sandin S, Lagiou P, Hilakivi-Clarke L, Trichopoulos D, Adami HO, et al. Dietary fat and breast cancer risk in the Swedish women's lifestyle and health cohort. Br J Cancer 2007; 97: 1570-1576. (PMID: 17940510) [Crossref]
54. Thiébaut AC, Chajès V, Gerber M, Boutron-Ruault MC, Joulin V, Lenoir G, et al. Dietary intakes of omega-6 and omega-3 polyunsaturated fatty acids and the risk of breast cancer. Int J Cancer 2009; 124: 924-931. (PMID: 19035453) [Crossref]
55. Sczaniecka AK, Brasky TM, Lampe JW, Patterson RE, White E. Dietary intake of specific fatty acids and breast cancer risk among postmenopausal women in the VITAL cohort. Nutr Cancer 2012; 64: 1131-1142. (PMID: 23137008) [Crossref]
56. Farvid MS, Cho E, Chen WY, Eliassen AH, Willett WC. Premenopausal dietary fat in relation to pre- and post-menopausal breast cancer. Breast Cancer Res Treat 2014; 145: 255-265. (PMID: 24715379) [Crossref]
57. Sieri S, Chiodini P, Agnoli C, Pala V, Berrino F, Trichopoulou A, et al. Dietary fat intake and development of specific breast cancer subtypes. J Natl Cancer Inst 2014; 106 : dju068. (PMID: 24718872) [Crossref]
58. Kim JH, Lee J, Jung SY, Kim J. Dietary Factors and Female Breast Cancer Risk: A Prospective Cohort Study. Nutrients 2017; 9 : 1331. (PMID: 29215604) [Crossref]
59. Park YM, White AJ, Nichols HB, O'Brien KM, Weinberg CR, Sandler DP. The association between metabolic health, obesity phenotype and the risk of breast cancer. Int J Cancer 2017; 140: 2657-2666. (PMID: 28268252) [Crossref]
60. Sellem L, Srour B, Guéraud F, Pierre F, Kesse-Guyot E, Fiolet T, et al. Saturated, mono- and polyunsaturated fatty acid intake and cancer risk: results from the French prospective cohort NutriNet-Santé. Eur J Nutr 2019; 58: 1515-1527. (PMID: 29616321) [Crossref]
61. Xia H, Ma S, Wang S, Sun G. Meta-Analysis of Saturated Fatty Acid Intake and Breast Cancer Risk. Medicine (Baltimore) 2015; 94: e2391. (PMID: 26717389) [Crossref]

62. Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, et al. Types of dietary fat and breast cancer: a pooled analysis of cohort studies. Int J Cancer 2001; 92: 767-774. (PMID: 11340585) [Crossref]
63. Boyd NF, Stone J, Vogt KN, Connelly BS, Martin LJ, Minkin S. Dietary fat and breast cancer risk revisited: a meta-analysis of the published literature. Br J Cancer 2003; 89: 1672-1685. (PMID: 14583769) [Crossref]
64. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008; 371: 569-578. (PMID: 18280327) [Crossref]
65. Travis RC, Key TJ. Oestrogen exposure and breast cancer risk. Breast Cancer Res 2003; 5: 239-247. (PMID: 12927032) [Crossref]
66. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. Nat Rev Cancer. 2015; 15: 484-498. (PMID: 26205341) [Crossref]
67. Andarawewa KL, Boulay A, Masson R, Mathelin C, Stoll I, Tomasetto C, et al. Dual stromelysin-3 function during natural mouse mammary tumor virus-ras tumor progression. Cancer Res 2003; 63: 5844-5849. (PMID: 14522908) [Crossref]
68. Dirat B, Bochet L, Dabek M, Daviaud D, Dauvillier S, Majed B, et al. Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion. Cancer Res 2011; 71: 2455-2465. (PMID: 21459803) [Crossref]
69. Wang YY, Lehuédé C, Laurent V, Dirat B, Dauvillier S, Bochet L, et al. Adipose tissue and breast epithelial cells: a dangerous dynamic duo in breast cancer. Cancer Lett 2012; 324: 142-151. (PMID: 22643115) [Crossref]
70. Rio MC, Dali-Youcef N, Tomasetto C. Local adipocyte cancer cell paracrine loop: can «sick fat» be more detrimental? Horm Mol Biol Clin Investig 2015; 21: 43-56. (PMID: 25781551) [Crossref]
71. Vandevijvere S, Chow CC, Hall KD, Umali E, Swinburn BA. Increased food energy supply as a major driver of the obesity epidemic: a global analysis. Bull World Health Organ 2015; 93: 446-456. (PMID: 26170502) [Crossref]
72. Te Morenga LA, Howatson AJ, Jones RM, Mann J. Dietary sugars and cardiometabolic risk: systematic review and meta-analyses of randomized controlled trials of the effects on blood pressure and lipids. Am J Clin Nutr 2014; 100: 65-79. (PMID: 24808490) [Crossref]
73. Forouhi NG, Sharp SJ, Du H, van der A DL, Halkjaer J, Schulze MB, et al. Dietary fat intake and subsequent weight change in adults: results from the European Prospective Investigation into Cancer and Nutrition cohorts. Am J Clin Nutr 2009; 90: 1632-1641. (PMID: 19828709) [Crossref]
74. Chaput JP, Tremblay A, Rimm EB, Bouchard C, Ludwig DS. A novel interaction between dietary composition and insulin secretion: effects on weight gain in the Quebec Family Study. Am J Clin Nutr 2008; 87: 303-309. (PMID: 18258618) [Crossref]
75. Suji M, Tamai Y, Wada K, Nakamura K, Hayashi M, Takeda N, et al. Associations of intakes of fat, dietary fiber, soy isoflavones, and alcohol with levels of sex hormones and prolactin in premenopausal Japanese women. Cancer Causes Control 2012; 23: 683-689. (PMID: 22399233) [Crossref]
76. Rose DP. Effects of dietary fatty acids on breast and prostate cancers: evidence from in vitro experiments and animal studies. Am J Clin Nutr 1997; 66(6 Suppl): 1513-1522. (PMID: 9394709) [Crossref]
77. Hardy S, El-Assaad W, Przybytkowski E, Joly E, Prentki M, Langelier Y. Saturated fatty acid-induced apoptosis in MDA-MB-231 breast cancer cells. A role for cardiolipin. J Biol Chem 2003; 278: 31861-31870. (PMID: 12805375) [Crossref]
78. Riccardi G, Giacco R, Rivellese AA. Dietary fat, insulin sensitivity and the metabolic syndrome. Clin Nutr 2004; 23: 447-456. (PMID: 15297079) [Crossref]
79. Farnetti S, Malandrino N, Luciani D, Gasbarrini G, Capristo E. Food fried in extra-virgin olive oil improves postprandial insulin response in obese, insulin-resistant women. J Med Food 2011; 14: 316-321. (PMID: 21142948) [Crossref]
80. Rose DP, Connolly JM, Coleman M. Effect of omega-3 fatty acids on the progression of metastases after the surgical excision of human breast cancer cell solid tumors growing in nude mice. Clin Cancer Res 1996; 2: 1751-1756. (PMID: 9816126) [Crossref]
81. Welsch CW. Review of the effects of dietary fat on experimental mammary gland tumorigenesis: role of lipid peroxidation. Free Radic Biol Med 1995; 18: 757-773. (PMID: 7750800) [Crossref]
82. Hardman WE, Munoz J Jr, Cameron IL. Role of lipid peroxidation and antioxidant enzymes in omega 3 fatty acids induced suppression of breast cancer xenograft growth in mice. Cancer Cell Int 2002; 2: 10. (PMID: 12296973) [Crossref]
83. Sun H, Berquin IM, Edwards IJ. Omega-3 polyunsaturated fatty acids regulate syndecan-1 expression in human breast cancer cells. Cancer Res 2005; 65: 4442-4447. (PMID: 15899837) [Crossref]
84. Saadatian-Elahi M, Norat T, Goudable J, Riboli E. Biomarkers of dietary fatty acid intake and the risk of breast cancer: a meta-analysis. Int J Cancer 2004; 111: 584-591. (PMID: 15239137) [Crossref]
85. Kitahara CM, Berrington de González A, Freedman ND, Huxley R, Mok Y, Jee SH, et al. Total cholesterol and cancer risk in a large prospective study in Korea. J Clin Oncol 2011; 29: 1592-1598. (PMID: 21422422) [Crossref]
86. Danilo C, Frank PG. Cholesterol and breast cancer development. Curr Opin Pharmacol 2012; 12: 677-682. (PMID: 22867847) [Crossref]
87. Voisin M, de Medina P, Mallinger A, Dalenc F, Huc-Claustre E, Leignadier J, et al. Identification of a tumor-promoter cholesterol metabolite in human breast cancers acting through the glucocorticoid receptor. Proc Natl Acad Sci U S A 2017; 114: 9346-9355. (PMID: 29078321) [Crossref]
88. Nelson ER, Wardell SE, Jasper JS, Park S, Suchindran S, Howe MK, et al. 27-Hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology. Science 2013; 342: 1094-1098. (PMID: 24288332) [Crossref]
89. Griffin JD, Lichtenstein AH. Dietary Cholesterol and Plasma Lipoprotein Profiles: Randomized-Controlled Trials. Curr Nutr Rep 2013; 2: 274-282. (PMID : 24466502) [Crossref]
90. Ni H, Liu H, Gao R. Serum Lipids and Breast Cancer Risk: A Meta-Analysis of Prospective Cohort Studies. PLoS One 2015; 10: e0142669. (PMID: 26554382) [Crossref]
91. Ikonen E. Cellular cholesterol trafficking and compartmentalization. Nat Rev Mol Cell Biol 2008; 9: 125-138. (PMID : 18216769) [Crossref]
92. Barclay M, Skipski VP, Terebus-Kekish O, Merker PL, Cappuccino JG. Serum lipoproteins in rats with tumors induced by 9,10-dimethyl-1,2-benzanthracene and with transplanted Walker carcinosarcoma 256. Cancer Res 1967; 27: 1158-1167. (PMID: 6066623) [Crossref]

Original Article

Eur J Breast Health 2022; 18(2): 127-133
DOI: 10.4274/ejbh.galenos.2022.2021-12-1

Patient Satisfaction and Surgical Outcome After Oncoplastic Reconstruction following Radical Lumpectomy *Versus* Standard Lumpectomy: A Retrospective Cohort Study

Eyal Barkai[1], Yossi Namir[2], Orit Golan[3], Yoav Barnea[1,2], Ehud Arad[1,2], Tehillah S. Menes[1,4]

[1]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[2]Department of Plastic Surgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[3]Department of Breast Imaging, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[4]Department of General Surgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

ABSTRACT

Objective: Oncoplastic reconstruction (OR) enables widening of the indications for breast conserving therapy (BCT) and is redefining the limits of breast conservation. We examined the outcome and satisfaction of patients undergoing OR after radical lumpectomy (excision of more than 25% of the breast volume) and compared it to the outcome of women undergoing OR after standard lumpectomy.

Materials and Methods: A retrospective, cohort study, including all patients undergoing OR after BCT between 2009 and 2018, was conducted. The ratio of volume of excision to breast volume was calculated using imaging studies. The study group included women that had more than 25% of their breast volume removed. The remainder formed the control group. Demographic characteristics, oncological treatment, and operation properties were collected. We compared post-operative complications, margin status and need for further surgery, as well as patient satisfaction, evaluated using the BREAST-Q Questionnaire.

Results: One hundred and fifty women were included, of whom 24 (16%) comprised the study group with a mean breast volume reduction of 39%, while the remainder (mean volume reduction 8%) served as controls. Patient, tumor characteristics and treatment were comparable. There was a non-significant higher proportion of women in the radical group that underwent a second operation due to complications or positive margins [4/24 (16.7%) vs. 14/126 (11%), p = 0.4). Physical well-being was similar but satisfaction with breasts and with outcome was slightly lower for the study group. These differences did not reach statistical significance.

Conclusion: Surgical outcome and patient satisfaction in women undergoing very extensive breast resections with OR are comparable to standard resections.

Keywords: Oncoplastic reconstruction; radical lumpectomy; BREAST-Q; breast conserving therapy; patient satisfaction

Cite this article as: Barkai E, Namir Y, Golan O, Barnea Y, Arad E, Menes TS. Patient Satisfaction and Surgical Outcome After Oncoplastic Reconstruction following Radical Lumpectomy Versus Standard Lumpectomy: A Retrospective Cohort Study. Eur J Breast Health 2022; 18(2): 127-133

Key Points

- The ability to reconstruct the breast using oncoplastic techniques, allows for extension of the indications for breast conservation.
- Outcome of radical lumpectomies (removal of more than 25% of breast volume) was compared to outcome of standard lumpectomies with oncoplastic reconstruction.
- Surgical outcome and patient satisfaction were comparable in women undergoing radical vs. standard lumpectomy.

Corresponding Author:
Tehillah S. Menes; Tehillah.menes@sheba.health.gov.il

Received: 14.12.2021
Accepted: 19.01.2022
Available Online Date: 01.04.2022

Introduction

Multiple prospective randomized trials reported similar disease-free and overall survival for breast conserving therapy (BCT) and mastectomy. As a result, BCT became the standard of care for patients with early breast cancer (1, 2). Nevertheless, some contraindications for BCT remain. These include multifocal breast cancer (at least two tumor foci in the same quadrant), multicentric breast cancer (at least two foci in different breast quadrants) (3) and large tumor to breast size ratio. The concern in these cases is a higher risk of recurrence and inferior cosmetic results (4). With the introduction of immediate reconstruction and collaboration between Breast and Plastic surgeons (oncoplastic surgery), cosmetic results following BCT have improved (5, 6), especially in large resections. The advantages of oncoplastic surgery include wider surgical margins (7) more efficient post-operative radiation treatment, especially in large and fatty breasts (8, 9), and improved oncologic and aesthetic outcomes (10-12).

As oncoplastic surgery minimizes breast deformation following wide excisions, it allows surgeons to "push the limits" and apply BCT in very extensive tumors and has re-defined the limits of breast conservation. Clough classified oncoplastic procedures according to the volume of excision (13). He defined removal of up to 20% of the volume as level I excision and removal of 20%–50% as level II excision. Level II excisions require more advanced oncoplastic techniques. Silverstein coined the term "extreme oncoplasty" for cases defined as "a patient who in most physicians' opinions requires a mastectomy" but underwent BCT with oncoplastic reconstruction (OR) (14). Several studies (14-16) reported outcomes of OR in selected patients with multifocal/multicentric tumors or a tumor that spanned more than 5 cm. The definition of Extreme Oncoplastic surgery used in all these reports does not take into consideration the breast size of the patient and may include cases that are within the standard indications for BCT with OR. The main factor that effects cosmetic outcome and need for OR is the proportion of volume excised (17, 18). Based on Clough's classification, we chose the proportion of volume removed to define the group of women undergoing extensive excisions. However, we chose the cutoff of 25% to define the term radical lumpectomy to include only the most extensive excisions that definitely required advanced oncoplastic techniques. The purpose of the current study was to examine the outcome of women undergoing radical lumpectomies with immediate OR, and to assess if it is comparable to the outcome of patients undergoing OR following standard lumpectomies.

Materials and Methods

This retrospective, cohort study was approved by the Institutional Review Board and Ethics Committee of Tel Aviv University (TLV-17-0453). All consecutive breast cancer patients undergoing BCT with OR by a team of general and plastic surgeons, between the years 2009 and 2018 in our medical center, were included in the study.

The patients were divided into two groups based on the extent of tissue resection. The study group included patients that had a "radical lumpectomy" whereas the control group included patients that had a standard lumpectomy excision.

Radical lumpectomy was defined as an excision of more than 25% of the breast volume. This was determined by dividing the calculated volume of resection by the calculated breast volume. The volume of resection was calculated from the imaging at the time of diagnosis or at the time of needle localization prior to surgery using the formula for calculation of a sphere volume:

$$v = \frac{4}{3}\pi r^3$$

; where r is half of the largest diameter of the tumor as visualized on imaging.

The volume of the breast was calculated using Kalbhen's formula (19):

$$v = \frac{\pi}{4} * h * w * c$$

Where w is the lateral-to medial longest dimension on cranio-caudal (CC) view, h is the anterior to posterior longest dimension (both w and h are estimated from the mammographic images), and c is the compression thickness of the breast as routinely reported by the mammography technician in the mammography report. As the compression thickness varies with the degree of compression, we used all measurements of the volume calculation from one exam. Most mammograms were done in our center using Hologic Selenia digital mammography system (Bedford, MA, USA).

When the ratio of the excision volume divided by the breast volume was larger than 0.25, the case was defined as a radical lumpectomy and allocated to the study group.

For both groups, the data collected included demographic and tumor characteristics, treatment details, operations properties, complications and histopathological findings. Intraoperative assessment of the margins was not routinely done due to the extensive analyses needed to rule out margin involvement. Follow-up time was defined as time elapsed between the dates of the surgery and the phone questionnaire. Patient satisfaction was evaluated using the BREAST-Q questionnaire (20). This questionnaire was developed to create a patient-reported outcome measure that would provide essential information about the impact and effectiveness of breast surgery. The BREAST-Q has a modular, procedure-specific structure with scales that evaluate both satisfaction and quality of life. Psychometric evaluation reveals high reliability, validity and responsiveness to surgical intervention across all scales (21). The reconstruction module is comprised of nine parts; each part includes a scale of up to 5 answers. In this study, parts 1, 3, 4 and 6 in the reconstruction module questionnaire were used.

All consecutive patients were contacted by phone, and asked to consent to be interviewed by investigators other than the treating surgeons. The questionnaire was filled out over the phone. Women were excluded from this part of the study if they had language limitations, or if they ultimately underwent a completion mastectomy because of positive margins.

The characteristics of the two groups were compared using the student's t-test for continuous variables and chi-square or Fisher's exact test for parametric variables. For analysis purpose the module's results were transformed to a normal scale of 100 points as recommended by the creators of the questionnaire.

Linear regression models were created in order to examine the association between extent of resection and patient satisfaction while controlling for possible confounders. Four models were created for the four outcomes that were assessed by the questionnaire. All tests were two-sided and a $p<0.05$ was considered significant. Statistical analysis

was completed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA).

Results

One hundred and sixty-eight patients underwent BCT with immediate OR during the study period. After excluding patients with benign disease, patients who passed away, and two women for whom extent of excision could not be determined, 150 women remained in the study. Patient and tumor characteristics are summarized in Table 1.

Table 1. Cohort characteristics

	Standard (n = 126)	Radical (n = 24)	*p*-value
Mean follow up, years (SD)	2.1 (1.8)	1.2 (2.3)	0.04
Mean age, years (SD)	52.6 (12)	52.9 (9)	0.9
Mean BMI (SD)	26.8 (5.1)	26.8 (6.5)	0.9
Smoking history, n (%)			
No	59 (66)	13 (68)	
Current	18 (20)	3 (16)	
Past	13 (14)	3 (16)	0.9
Grade, n (%)			
1	9 (7)	0	
2	44 (36)	12 (50)	
3	55 (45)	10 (42)	0. 5
Lobular, other, unknown	14 (11)	2 (8)	
Receptor status, n (%)			
Luminal	91 (74)	19 (79)	
Triple negative	8 (7)	2 (8)	0.7
HER-2 positive	24 (20)	3 (13)	
T stage (at diagnosis), n (%)			
In situ	11 (9)	5 (22)	
1	48 (39)	7 (30)	
2	44 (36)	9 (39)	
3+	19 (17)	2 (11)	0.4
Unknown	4 (3)	1(4)	
Node positive at diagnosis	53 (43)	8 (33)	0.4
Neoadjuvant treatment, n (%)			
None	71 (58)	13 (54)	
Chemotherapy	24 (20)	7 (29)	
Hormonal	10 (8)	1 (4)	0.7
Chemotherapy and HER-2neu targeted therapy	17 (14)	3 (13)	
Localization type, n (%)			
None	12 (10)	0	
Ultrasound	48 (38)	7 (29)	
Mammography	49 (39)	14 (58)	
MRI	8 (6)	1 (4)	0.3
Combination	8 (6)	2 (8)	

Twenty-four (16.7%) cases were included in the radical lumpectomy group; the mean ratio of excision volume to breast volume was 0.39. The control group consisted of 126 (84%) women with a mean volume ratio of 0.08.

The mammographic preoperative localization of one of the radical lumpectomy patients is depicted in Figure 1. Pre-operative and post-radiation images are depicted in Figure 2.

Table 1. continued

	Standard (n = 126)	Radical (n = 24)	*p*-value
Mean number of localizing needles (SE)*	2 (0.1)	3.6 (0.2)	<0.001
Type of reconstruction, n (%)			
Reduction	81 (64)	13 (54)	
Reduction with mastopexy	4 (3)	0	
Mastopexy	37 (29)	11 (46)	
Augmentation	2 (2)	0	0.7
Other	2 (2)	0	
Median specimen weight, grams (SE)*	94 (10)	177 (26)	0.005**
Margin status, n (%)			
Involved or close	15 (12)	6 (25)	0.2
Re-operation, n (%)			
Positive margin	10 (8)	2 (8)	
Complication (debridement, closure of dehiscence)	4 (3)	2 (8)	0. 4
Complications (total), n (%)	11 (9)	3 (13)	
Infection	7 (6)	1 (4)	
Dehiscence; necrosis requiring surgery	4 (3)	2 (8)	0.5
Adjuvant treatment, n (%)			
Chemotherapy	20 (16)	4 (17)	0.9
Chemotherapy and HER-2neu targeted therapy	4 (3)	0	
Hormonal	99 (81)	17 (71)	0.3
Adjuvant radiation, n (%)	112 (92)***	24 (100)	0.4
Recurrence, n (%)			
Loco-regional	7 (6)	2(8)	
Distant	3 (3)	0	0.2
Mortality	6(5)	1(4)	0.8

*Lumpectomy specimen only, reduction not included.

**Mann-Whitney U test.

***Recommendation for radiation after lumpectomy was based on women's' characteristics (age and comorbidities) and final pathology.

BMI: Body Mass Index; HER-2: human epidermal growth factor receptor 2; MRI: magnetic resonance imaging; SE: standard error; SD: standard deviation; n: number

The two groups were comparable in respect to demographic and tumor characteristics, as well as neoadjuvant and adjuvant treatment (Table 1). The T stage was similar in both groups. However, diagnosis of ductal carcinoma *in situ* (DCIS) was more prevalent in the study group (n = 5, 22%) compared to the control group (n = 11) (9).

The mean follow-up time was slightly longer for the control group (2.1±1.8 years vs. 1.2±2.3 in the study group). The mean number of needles inserted to mark the tumor for excision was higher in the study group, (3.6±0.2 compared to 2±0.1 in the control group). The median specimen weight was higher in the study group (177±26 grams vs. 94±10 in the control group). In both groups, most women underwent OR using breast reduction techniques (n = 13; 54% of the study group; and n = 81; 64% in the control group). Most women (n = 143, 95%) had a bilateral procedure. In 17 (11%) patients, this was done for a bilateral cancer or a high-risk lesion in the contralateral breast, and in the remainder of cases, the contralateral procedure was done in order to achieve symmetry. Close or positive pathology margins were found in 6 (25%) women in the study group compared to 15 (12%) in the control group); this difference was not statistically significant. Two patients (8%) in the radical lumpectomy group underwent re-lumpectomy because of involved margins, whereas in the standard lumpectomy group, 10 patients (8%) had an additional operation. Seven required a re-lumpectomy, three required a mastectomy and one patient required a sentinel lymph node biopsy. Two women with involved margins were planned to undergo a repeat surgery (mastectomy) after completing adjuvant chemotherapy, but subsequently refused.

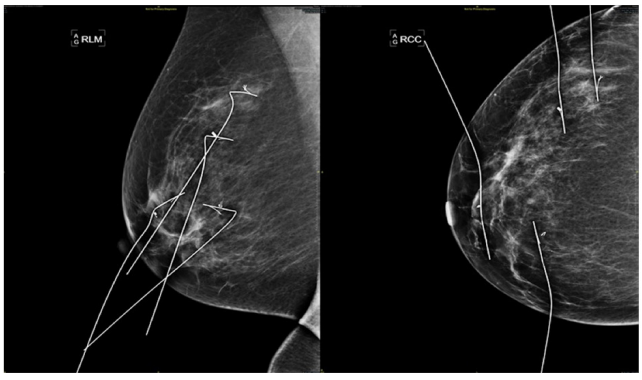

Figure 1. Mammographic preoperative localization of breast tumor prior to radical lumpectomy. The patient completed neoadjuvant treatment for extensive luminal infiltrating ductal carcinoma with nodal involvement. She underwent radical lumpectomy, sentinel node biopsy and oncoplastic reconstruction. Pathology showed residual DCIS and atypical ductal hyperplasia with clear margins, and negative sentinel lymph nodes

DCIS: ductal carcinoma in situ

Three patients (13%) in the radical lumpectomy group experienced complications: two (8%) required revision of the surgery within one month of the original surgery; one underwent debridement and closure of the wound and the other required revision because of nipple congestion. In the control group, 11 (9%) patients had a complication, four (3%) of them requiring revisional surgery; three underwent debridement, one of them of the nipple and one closure of wound dehiscence.

The BREAST-Q questionnaire was completed by 95 (63%) patients, 15 (63%) of whom were in the study group and the remainder in the control group (80; 64%), (Table 2).

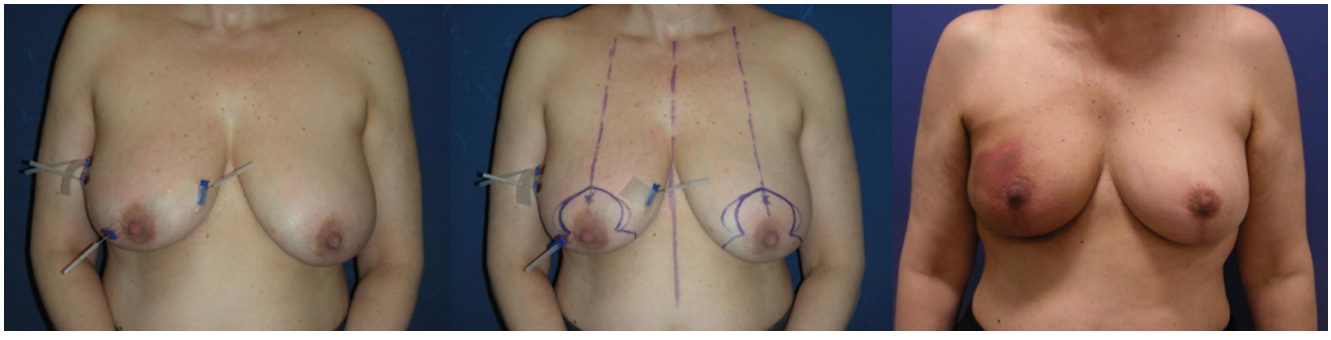

Figure 2. From left to right: Preoperative needle localization **(a)**, markings **(b)** and cosmetic result one-month post-radiation **(c)** of a patient undergoing radical lumpectomy

Table 2. Patient satisfaction after breast conserving surgery with oncoplastic reconstruction as assessed by the BREAST-Q questionnaire (women who had a second surgery were included unless final surgery was a mastectomy)

	Standard lumpectomy (n = 80)	Radical (n = 15)	*p*-value
Mean time to survey, years (SE)	3.3 (0.3)	2.2 (0.5)	0.08
Mean Satisfaction with Breasts score (SE)	73 (2.1)	63 (6.1)	0.08
Mean Satisfaction with Outcome score (SE)	81 (2.5)	73 (6)	0.16
Mean Psycho Social Well-being score (SE)	82 (2.1)	78 (4.9)	0.45
Mean Physical Well-being: Chest score (SE)	72 (2.1)	74 (4.9)	0.76

SE: standard error; n: number

Based on the BREAST-Q, satisfaction with breasts and with outcomes were slightly lower for the group undergoing radical lumpectomy. However, these differences did not reach statistical significance. On multivariate linear regression analysis (Table 3), no association was found between extent of surgery, patient characteristics and the different outcomes assessed by the modules of the BREAST-Q.

Discussion and Conclusion

We report the results of women undergoing radical lumpectomy with immediate OR. The characteristics of the women and their tumors were similar to those of women undergoing standard lumpectomy with immediate OR. We found that margin status, complication rates and patient satisfaction were comparable to women undergoing standard lumpectomy with immediate OR. Since Silverstein first coined the term "extreme oncoplasty" in 2015 (14), suggesting the concept of OR in patients that "normally require a mastectomy", several other studies have confirmed the feasibility of extreme oncoplastics, and reported long-term outcomes (18, 22). Koppiker et al.(16) reported results in 39 women undergoing extreme OR followed by radiation. There was no comparison group in this report. They found no major complications, and three minor complications (seroma and wound healing problems treated conservatively). The results of the questionnaire, collected 12 months after the operation, showed good satisfaction with breasts (78.0±16.6) and with outcome (85.7±13.7) and high psychosocial (90.8±11.5) and sexual wellbeing (75.8±11.7). Crown et al. (15) reported the results of 111 women undergoing extreme OR. In this study the complication rate was 16%, with 2% having revisional surgery. More than half needed a second surgery for positive margins, usually a re-excision. This high proportion maybe explained by the limited use of neoadjuvant treatment in this cohort (5%). Recurrence rates among women completing radiation were low (1.1%). Cosmetic outcome was evaluated by the operating surgeons, using the Harvard Breast Cosmesis Scale. Good to excellent cosmetic outcome was reported in 95% of the patients, with patients undergoing a second surgery and those experiencing complications having slightly lower rates. Acea Nebril et al. (23) assessed patient

Table 3. Multivariate analysis: satisfaction with breasts; satisfaction with outcome; psychosocial well-being; physical well-being

	B	Standard error	Standardized B	*p*-value
Satisfaction with breasts				
Age, years	-0.14	0.19	-0.10	0.49
Smoking	-5.85	5.57	-0.16	0.30
BMI	0.10	0.50	0.03	0.85
Radical lumpectomy	-5.32	6.02	-0.13	0.38
Specimen weight, grams	-0.03	0.03	-0.14	0.40
Time between surgery and questionnaire, days	-0.00	0.00	-0.13	0.39
Satisfaction with outcome				
Age, years	-0.42	0.20	-0.30	0.04
Smoking	-8.53	5.70	-0.21	0.14
BMI	-0.29	0.51	-0.09	0.57
Radical lumpectomy	-5.92	6.17	-0.14	0.34
Specimen weight, grams	-0.00	0.03	-0.01	0.94
Time between surgery and questionnaire, days	-0.00	0.00	-0.11	0.48
Psychosocial well-being				
Age, years	-0.026	0.20	-0.18	0.20
Smoking	-10.59	5.87	-0.26	0.08
BMI	-0.12	0.53	-0.04	0.82
Radical lumpectomy	2.09	6.35	0.05	0.74
Specimen weight, grams	-0.06	0.03	-0.29	0.08
Time between surgery and questionnaire, days	0.00	0.00	0.11	0.45
Physical well-being: chest				
Age, years	0.13	0.21	0.09	0.55
Smoking	-1.47	6.28	-0.04	0.82
BMI	-0.18	0.54	-0.05	0.73
Radical lumpectomy	4.63	6.71	0.11	0.49
Specimen weight, grams	-0.04	0.03	-0.13	0.28
Time between surgery and questionnaire, days	0.00	0.01	0.13	0.41

BMI: Body Mass Index

satisfaction using the same questionnaire. They found that patients who underwent extreme oncoplastic breast conserving surgery had significantly greater satisfaction with their breasts (82.5% in the extreme oncoplastic group, 76.3% in the standard oncoplastic group), with higher outcome scores (88% vs. 82.1%) and higher psychological well-being scores (78.7% vs. 67.2%). These reports do not take into consideration the breast size of the patient. The volume of the remaining breast is crucial. For example, removal of a 5 cm tumor in a D-cup breast is smaller than the excision of breast tissue in an average breast reduction. The concept of multicentric disease can be misleading as well, as two tumors located in different quadrants, (for example at 2 and 4 o'clock) are considered as multicentric disease, yet the distance between the two may enable BCT without a negative impact on cosmetic outcome even without OR. We chose therefore, to use the ratio of volume of excision to calculated breast volume in order to define the extent of excision and coined the term "Radical lumpectomy" to describe OR for lumpectomies involving the excision of more than 25% of the breast volume. This definition is more radical than the "extreme Oncoplastic reconstruction" definition, which explains our relatively small study group. Importantly, we used standardized definitions for the assessment of the excision and breast volumes, making this definition reproducible.

This study has several limitations. It is a retrospective study of patients from a single institution. The number of patients in the study group is small, which may limit the power of the study to find small differences in the different outcomes. The women were approached at different follow-up times from the surgery with the study group having a significantly shorter median follow-up time compared to the control group. As cosmetic results change over time, the difference in follow-up time may have had an impact on patient satisfaction. Although volumes of excision and breast were calculated with standard formulae, the measurement of the different components of the formula is operator dependent. This may compromise the reproducibility of these calculations. The BREAST-Q questionnaire was completed over the phone by 63% of the women in the study, which may point to a selection bias. This might have impacted the answers, especially in more of the intimate questions regarding self-image; we tried to limit this concern by approaching the patients by investigators other than the treating surgeons. It is assumed that this limitation is non-differential and affected the two groups similarly and thus should not impact the results of the study.

In conclusion, in this preliminary study, examining outcome of oncoplastic reconstruction after radical lumpectomies, which was defined as removal of more than 25% of the breast volume for the purpose of this study, surgical outcome and patient satisfaction were comparable in the study and control groups. Long term outcome and oncological safety need to be examined.

Ethics Committee Approval: This retrospective, cohort study was approved by the Tel Aviv Sourasky Ethics Committee (approval no: TLV-17-0453).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

References

1. Hartmann-Johnsen OJ, Kåresen R, Schlichting E, Nygård JF. Survival is better after breast conserving therapy than mastectomy for early stage breast cancer: a registry-based follow-up study of Norwegian women primary operated between 1998 and 2008. Ann Surg Oncol 2015; 22: 3836-3845. (PMID: 25743325) [Crossref]
2. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002; 347: 1227-1232. (PMID: 12393819) [Crossref]
3. Middleton LP, Vlastos G, Mirza NQ, Eva S, Sahin AA. Multicentric mammary carcinoma: evidence of monoclonal proliferation. Cancer 2002; 94: 1910-1916. (PMID: 11932891) [Crossref]
4. Nijenhuis MV, Rutgers EJ. Conservative surgery for multifocal/multicentric breast cancer. Breast 2015; 24(Suppl 2): 96-99. (PMID: 26303986) [Crossref]
5. Clough KB, Cuminet J, Fitoussi A, Nos C, Mosseri V. Cosmetic sequelae after conservative treatment for breast cancer: classification and results of surgical correction. Ann Plast Surg 1998; 41: 471-481. (PMID: 9827948) [Crossref]
6. D'Aniello C, Grimaldi L, Barbato A, Bosi B, Carli A. Cosmetic results in 242 patients treated by conservative surgery for breast cancer. Scand J Plast Reconstr Surg Hand Surg 1999; 33: 419-422. (PMID: 10614751) [Crossref]
7. Kaur N, Petit JY, Rietjens M, Maffini F, Luini A, Gatti G, et al. Comparative study of surgical margins in oncoplastic surgery and quadrantectomy in breast cancer. Ann Surg Oncol 2005; 12: 539-545. (PMID: 15889210) [Crossref]
8. Moody AM, Mayles WP, Bliss JM, A'Hern RP, Owen JR, Regan J, et al. The influence of breast size on late radiation effects and association with radiotherapy dose inhomogeneity. Radiother Oncol 1994; 33: 106-112. (PMID: 7708953) [Crossref]
9. Neal AJ, Torr M, Helyer S, Yarnold JR. Correlation of breast dose heterogeneity with breast size using 3D CT planning and dose-volume histograms. Radiother Oncol 1995; 34: 210-218. (PMID: 7631027) [Crossref]
10. Crown A, Wechter DG, Grumley JW. Oncoplastic breast-conserving surgery reduces mastectomy and postoperative re-excision rates. Ann Surg Oncol 2015; 22: 3363-3368. (PMID: 26208579) [Crossref]
11. Santos G, Urban C, Edelweiss MI, Zucca-Matthes G, de Oliveira VM, Arana GH, et al. Long-term comparison of aesthetical outcomes after oncoplastic surgery and lumpectomy in breast cancer patients. Ann Surg Oncol 2015; 22: 2500-2508. (PMID: 25519931) [Crossref]
12. Crown A, Handy N, Rocha FG, Grumley JW. Oncoplastic reduction mammaplasty, an effective and safe method of breast conservation. Am J Surg 2018; 215: 910-915. (PMID: 29548531) [Crossref]
13. Clough KB, Kaufman GJ, Nos C, Buccimazza I, Sarfati IM. Improving breast cancer surgery: a classification and quadrant per quadrant atlas for oncoplastic surgery. Ann Surg Oncol 2010; 17: 1375-1391. (PMID: 20140531) [Crossref]
14. Silverstein MJ, Savalia N, Khan S, Ryan J. Extreme oncoplasty: breast conservation for patients who need mastectomy. Breast J 2015; 21: 52-59. (PMID: 25583035) [Crossref]

15. Crown A, Laskin R, Rocha FG, Grumley J. Extreme oncoplasty: expanding indications for breast conservation. Am J Surg 2019; 217: 851-856. (PMID: 30771865) [Crossref]

16. Koppiker CB, Noor AU, Dixit S, Busheri L, Sharan G, Dhar U, et al. Extreme oncoplastic surgery for multifocal/multicentric and locally advanced breast cancer. Int J Breast Cancer 2019; 2019: 4262589. (PMID: 30915240) [Crossref]

17. Dixon JM, Macaskill EJ. Breast-conserving surgery: the balance between good cosmesis and local control. In: Breast Surgery: A Companion to Specialist Surgical Practice. 6th ed. 2019. p. 86-104. Available at: https://www.melbournebreastcancersurgery.com.au/wp-content/themes/ypo-theme/pdf/breast-conserving-surgery-the-balance-between-good-cosmesis-and-local-control.pdf [Crossref]

18. Mansell J, Weiler-Mithoff E, Stallard S, Doughty JC, Mallon E, Romics L. Oncoplastic breast conservation surgery is oncologically safe when compared to wide local excision and mastectomy. Breast 2017; 32: 179-185. (PMID: 28214785) [Crossref]

19. Kalbhen CL, McGill JJ, Fendley PM, Corrigan KW, Angelats J. Mammographic determination of breast volume: comparing different methods. AJR. Am J Roentgenol 1999; 173: 1643-1649. (PMID: 10584814) [Crossref]

20. Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. Plast Reconstr Surg 2009; 124: 345-353. (PMID: 19644246) [Crossref]

21. Cohen WA, Mundy LR, Ballard TN, Klassen A, Cano SJ, Browne J, et al. The BREAST-Q in surgical research: a review of the literature 2009-2015. J Plast Reconstr Aesthet Surg 2016; 69: 149-162. (PMID: 26740288) [Crossref]

22. Pearce BCS, Fiddes RN, Paramanathan N, Chand N, Laws SAM, Rainsbury RM. Extreme oncoplastic conservation is a safe new alternative to mastectomy. Eur J Surg Oncol 2020; 46: 71-76. (PMID: 31543385) [Crossref]

23. Acea Nebril B, García Novoa A, Polidorio N, Cereijo Garea C, Bouzón Alejandro A, Mosquera Oses J. Extreme oncoplasty: The last opportunity for breast conservation-Analysis of its impact on survival and quality of life. Breast J 2019; 25: 535-536. (PMID: 30964211) [Crossref]

Original Article

Eur J Breast Health 2022; 18(2): 134-140
DOI: 10.4274/ejbh.galenos.2022.2021-8-3

Assessment of Stromal Elastin Fibers in Breast Cancer and Fibroadenomas: Is There a Correlation With Ultrasound Elastography Findings?

Nurşen Toprak[1], İbrahim Aras[2], Osman Toktaş[3], Adem Yokuş[1], Ali Mahir Gündüz[1]

[1]Department of Radiology, Van Yüzüncü Yıl University Faculty of Medicine, Van, Turkey
[2]Department of Pathology, Van Yüzüncü Yıl University Faculty of Medicine, Van, Turkey
[3]Department of General Surgery, Van Yüzüncü Yıl University Faculty of Medicine, Van, Turkey

ABSTRACT

Objective: The stiffness of a breast lesion provides information on the likelihood of malignancy. The most important factor affecting this stiffness is the composition of the extracellular matrix (ECM). The aim of this study was to assess the elastin fiber contents of malignant breast lesions and fibroadenomas and investigate any relationship between the shear wave velocity (SWV) measured by ultrasonography, and the elastin fiber content of lesions.

Materials and Methods: Consecutive patients with breast lesions were enrolled. The SWV values of the lesions were analyzed. Histopathological analysis of elastin in excised lesions was performed by the method of Shivas and Douglas. Breast cancer patients were reviewed according to their lymph node status and tumor diameter. The relationship between SWV value and tissue elastin fiber score was analyzed. The correlation between breast cancer grade and elastin fiber score in malignant lesions was investigated.

Results: A total of 167 consecutive breast lesions in 167 patients were included in this study (75 invasive cancer, 92 fibroadenomas). High elastic fiber score was significantly more common (p = 0.001) in malignant lesions (n = 61; 81.3%) than fibroadenomas (n = 13; 14.1%). There was a negative correlation between the mean SWV and the elastin fiber score of fibroadenomas (p = 0.001). A low grade in breast cancer was associated with high elastin fiber score (p = 0.01).

Conclusion: Malignant lesions tend to have higher elastin fiber scores than fibroadenomas. Elastin fiber assessment may provide additional prognostic information in malignant lesions. Changes in elastin fiber content may account for the variation in elasticity in fibroadenomas.

Keywords: ARFI elastography; breast cancer; elastin fiber; fibroadenoma

Cite this article as: Toprak N, Aras İ, Toktaş O, Yokuş A, Gündüz AM. Assessment of Stromal Elastin Fibers in Breast Cancer and Fibroadenomas: Is There a Correlation With Ultrasound Elastography Findings? Eur J Breast Health 2022; 18(2): 134-140

Key Points

- This study is a novel method for breast imaging that assesses the elasticity of a range of breast lesions.
- Although the effect of ECM components on breast lesion stiffness is important, there is little research on this subject.
- Elastin fiber is a protein that can change the stiffness of fibroadenomas. Therefore, it can be used to differentiate fibroadenomas from malignant lesions.
- Since the elastin fiber score is higher in low-grade breast cancers, it may have some use as a prognostic marker, if sufficient evidence is available.

Introduction

The extracellular matrix (ECM) is a complex network that is mainly comprised of interstitial collagen, elastin fibers, fibronectin, and many types of proteoglycans (1). An excessive accumulation of the components of the ECM is observed in breast carcinoma (2). This accumulation in invasive cancers causes stiffness of the tissue and thus promotes tumor invasion and metastasis (3).

Some studies have shown that collagen fibers, the main protein in ECM, may play an important role in the stiffness of breast lesions (4, 5). Elastin fiber is the second most important protein in the ECM and is responsible for the elasticity of the tissues. In a study investigating the relationship between ECM proteins and stromal stiffness, collagen fiber and elastin fiber were both associated with the stiffness of breast lesions (6). While earlier studies have investigated the relationship of collagen with tissue stiffness, there is no study investigating the role of elastin

Corresponding Author:
Nurşen Toprak; nursentoprak31@gmail.com

Received: 23.08.2021
Accepted: 31.01.2022
Available Online Date: 01.04.2022

in tissue stiffness (4, 5). Thus, the individual contribution of elastin fiber in the stiffness of breast lesions is still not entirely clear. Large aggregates of elastin fibers, a condition known as elastosis, are found in breast cancer stroma (1, 7, 8). Elastosis is usually associated with breast cancer, but it has also been reported to occur inconsistently in fibroadenoma (9).

In various breast pathologies, the most important radiological method to assess the stiffness or flexibility resulting from the differentiation of various proteoglycans in the ECM is ultrasound elastography (USE). In the literature, several studies have reported that shear wave elastography (SWE) showed good performance in assessing benign and malignant breast lesions. SWE is an objective and quantitative method for estimating tissue stiffness. Some studies have evaluated the correlation between SWE and ECM components in breast lesions (5, 6, 10, 11).

To the best of our knowledge, there is no study in the literature investigating the effect of elastin fiber content on stromal stiffness in, fibroadenomas and invasive breast cancer. The aim of this study was to investigate the relationship between elastin fiber content and the shear wave velocity (SWV), one of the parameters obtained from SWE, in fibroadenomas and breast cancer.

Materials and Methods

Patients

The study was conducted in the Breast Radiology Unit and Pathology Unit of the Van Yüzüncü Yıl University Faculty of Medicine from October 2018 to March 2019. The study was approved by our University Ethics Committee (decision number: 2020/03-09, date: 22/05/2020).

Retrospectively, patients with Breast Imaging Reporting and Data System (BI-RADS) 4-5 breast masses were included in the study. Patient consent was waived due to the retrospective nature of the study. An ultrasound (US)-guided, cutting needle biopsy was performed on all lesions, and histopathological results of the lesions were obtained. Patients with histopathological results diagnosing invasive breast cancer or fibroadenoma were included. Patients with breast lesions with other benign histopathology or diagnosed with ductal carcinoma *in situ* were excluded from the study.

Ultrasound and Shear Wave Elastography

US was performed by a radiologist with 10 years of experience in US and 5 years-experience with breast USE. Bandwidth linear array transducer probes of 14 MHz were used for US and 9 MHz probes for acoustic radiation force impulse (ARFI) elastography evaluation (Acuson-S2000; Siemens Medical Solutions, Mountain View, CA, USA).

Breast lesions detected by US, and following The American College of Radiology (ACR) BI-RADS criteria, were evaluated based on assessment of margin, shape, orientation, echo pattern, calcification, and posterior features (12).

In ARFI elastography, the virtual touch tissue quantification (VTTQ) option was used. During elastography, the parameters for the "breast" option were used with the "factory pre-set". A 5-mm-wide US probe at a frequency of 9 MHz was used to approach the lesion using gel. No pressure was applied to the skin. Split-screen display mode was used to obtain US and elastography images of the same location. When the lesion was visible on US, the patient was instructed to hold her breath, and elastography images were obtained. It is known that breast lesions show heterogeneous internal structure and in elastography images hard areas of the lesion appear white and soft areas black. The regions of interest (ROIs) on the VTTQ measuring 1 mm × 1 mm was used to provide related SWV values. Although the number of ROIs varies according to the lesion size, an equal number of ROIs were used to place the black (soft) and white (hard) areas in the virtual touch imaging. The ROIs were placed within the borders of the lesion, and the SWV values were automatically quantified in meters per second (m/s). The mean SWV value was obtained by averaging the SWV values measured. Lesion stiffness was measured by SWV imaging at up to 10 m/s.

Histopathological Examination and Elastosis Scoring

US-guided tru-cut biopsy was performed in breast lesions categorized as BI-RADS 4-5. For the tru-cut biopsy, a 14-gauge-thickness, 10-cm-long, fully automatic biopsy needle was used. The number of samples varied between 4–8 according to lesion size.

Elastin fibers are ECM components and are defined by their elasticity scores in breast lesions. The paraffin blocks of patients diagnosed with invasive ductal carcinoma and fibroadenoma were used for scoring elastin fibers. Four-micron thick sections were prepared and elastin stain was applied to all sections. Evaluation and scoring of elastin fiber content was evaluated by a pathologist, blinded to the US elastography results of the lesions. The amount of elastin fibers in the tumor stroma was scored (score: 0–3) according to the system of Shivas and Douglas (13). Tumors without elastin fibers were assigned a score of 0, those with thin elastin fibers or rim-shaped elastin around the duct were given a score of 1, lesions with thicker elastin fiber areas were assigned a score of 2, and those with large elastin fiber deposits in the tumor area were given a score of 3. The lesions were further categorized into two groups according to their elastin fiber content; those with a score of 0–1 were categorized as the low-score sub-group, and lesions with a score of 2–3 were categorized as the high-score sub-group. The pathologist who scored the elastin fiber content of the tumors was blinded to the other characteristics of the patients.

In addition, all benign lesions were analyzed according to their size by measuring the long axis diameter as either shorter than 2 cm or longer than 2 cm using. US images. The relationship between size and SWV and elasticity scores was analyzed. Malignant lesions were measured by ultrasonography in cm and lymph node status was investigated by US and positron emission tomography (PET). Malignant lesions were classified according to tumor diameter (under 2 cm as T1, 2–5 cm as T2, and >5 cm as T3). The relationship between tumor size and lymph node status with elastin scores was evaluated.

Histological grading was performed according to the Scarff-Bloom-Richardson system in malignant lesions (14). Grade 1–2 malignant lesions were considered as low grade, grade 3 malignant lesions as high grade.

Statistical Analysis

Descriptive statistics include mean and, standard deviations, and minimum and maximum values. A chi-square test was used for the distribution of elastosis scores in malignant lesions and fibroadenomas. Also, a chi-square test was used for the correlation of malignant lesion grade with elastin fiber scores. The Independent Samples t-test was used to compare the mean SWV between groups. The Statistical

Package for the Social Sciences software, version 13.0 was used for analysis (SPSS Inc., Chicago, IL, USA).

Results

Two hundred and fifty-five patients with a breast mass and with histopathological diagnosis were evaluated. Eighty-eight breast lesions that were diagnosed as proliferative and non-proliferative breast lesions, mastitis, and ductal carcinoma *in situ* (DCIS) were excluded. This resulted in a total of 167 patients being included in this study, subdivided into 92 (55.1%) with fibroadenoma and 75 (44.9%) with an invasive malignant breast mass. The mean age of the patients was 51.5±11.9 years in the malignancy group, and 33.6±12.3 years in the fibroadenoma group, which was significantly different (p = 0.001). Sixty-eight of the malignant lesions were invasive ductal cancer and seven were invasive lobular cancer. The mean SWV value was significantly greater at 6.10±1.6 m/s in the invasive cancer group compared to 3.32±1.0 m/s in the fibroadenoma group (p = 0.001). The SWV values in older patients with fibroadenoma was significantly greater (p<0.05) than in younger patients with fibroadenoma; <40 years old mean SWV 3.17±0.74 m/s vs above 40 years old: 3.61±1.36 m/s in patients aged >40 years.

The malignant lesions had significantly higher elastin fiber scores than fibroadenomas (p = 0.001) (Table 1 and Figures 1a and b). There was no correlation between the mean SWV value of malignant lesions and elastin fiber score (p = 0.175). However, low-grade lesions showed a higher elasticity score, and so elastin fiber score was found to be negatively correlated (p = 0.01) with grade of malignancy (Table 2). Malignant lesion size and lymph node status were not associated with the elastin fiber score (Table 3).

The mean SWV of fibroadenomas with low elastin fiber score was higher than the mean SWV of fibroadenomas with high elastin fiber score (p = 0.02) (Figures 2a–c, 3a–c and Table 4). A significant correlation was found between fibroadenomas size and elastin fiber score (p = 0.03). Fibroadenomas smaller than 20 mm in diameter were softer than ones with a larger diameter (>20 mm), and elastin fiber scores were higher (p = 0.001). Thus, there was a positive correlation between the size of fibroadenomas and the SWV, and an inverse correlation with the elastin fiber score (Table 5). However, no statistically significant correlation was found between breast cancer tumor size and elastin fiber score (p>0.05).

Discussion and Conclusion

This study has shown that the amount of elastin fiber in fibroadenomas was significantly less than that in malignant lesions. Furthermore, although the mean SWV value of malignant lesions was not correlated with the amount of elastin fiber present, the low SWV values of fibroadenomas was correlated with larger amounts of elastin fibers.

Elastin is an important ECM protein that provides elasticity to tissues and organs (1). Breast carcinoma cells stimulate the proliferation of stromal cells and promote elastin production (15). In breast cancer, elastin is present, both as individual fibers in the stroma and as large aggregates around the ducts or small blood vessels (7). The structural elements of tissues consist of structural proteins, including collagens, laminins, and elastin. During the tissue cycle, there is a balance between the formation and degradation of these proteins to ensure tissue health and homeostasis (1). Elastin and other ECM proteins interact with cancer cells (15, 16). Imbalances in the cycling of ECM proteins can lead to fibrosis, which can affect almost any organ or tissue. During fibrosis all structural elements, including collagen, laminin and elastin may be involved (1, 7). In this study, the lack of a significant correlation between the mean SWV value of malignant lesions and the elastin fiber score means that it is unreliable to use the elastin fiber score as a marker of SWV, possibly due to the effects of other ECM structural proteins on SWV measurements.

Chaming's et al. (17) reported that the stiffness of a breast invasive ductal carcinoma is associated with fibrosis. Also, connective tissue formation is increased in carcinomas (17-19). Lee et al. (10) revealed

Table 1. Elastin fiber scores according to histopathology

Elastin fiber score	Invasive cancer		Fibroadenoma	
	n (%)	*p*-value	n (%)	*p*-value
Low elastin score (0–1)	16 (21.3%)	0.001	79 (87%)	0.001
High elastin score (2–3)	59 (78.7%)		13 (13%)	
Total	75 (100%)		92 (100%)	

n: number

Table 2. Correlation of elastin fiber scores according to grade of invasive cancer

Elastin fiber score	Low grade invasive cancer n (%)	High grade invasive cancer n (%)	*p*-value
Low elastin score (0–1)	10 (16.1)	6 (46.2)	0.01
High elastin score (2–3)	52 (83.9)	7 (53.8)	
Total	62 (100)	13 (100)	

n: number

that malignant lesions have a harder structure than benign lesions and that the most important ECM protein providing this stiffness is collagen. As has been shown by this and earlier studies, malignant breast lesions also contain more elastin fiber than benign breast lesions (4, 20).

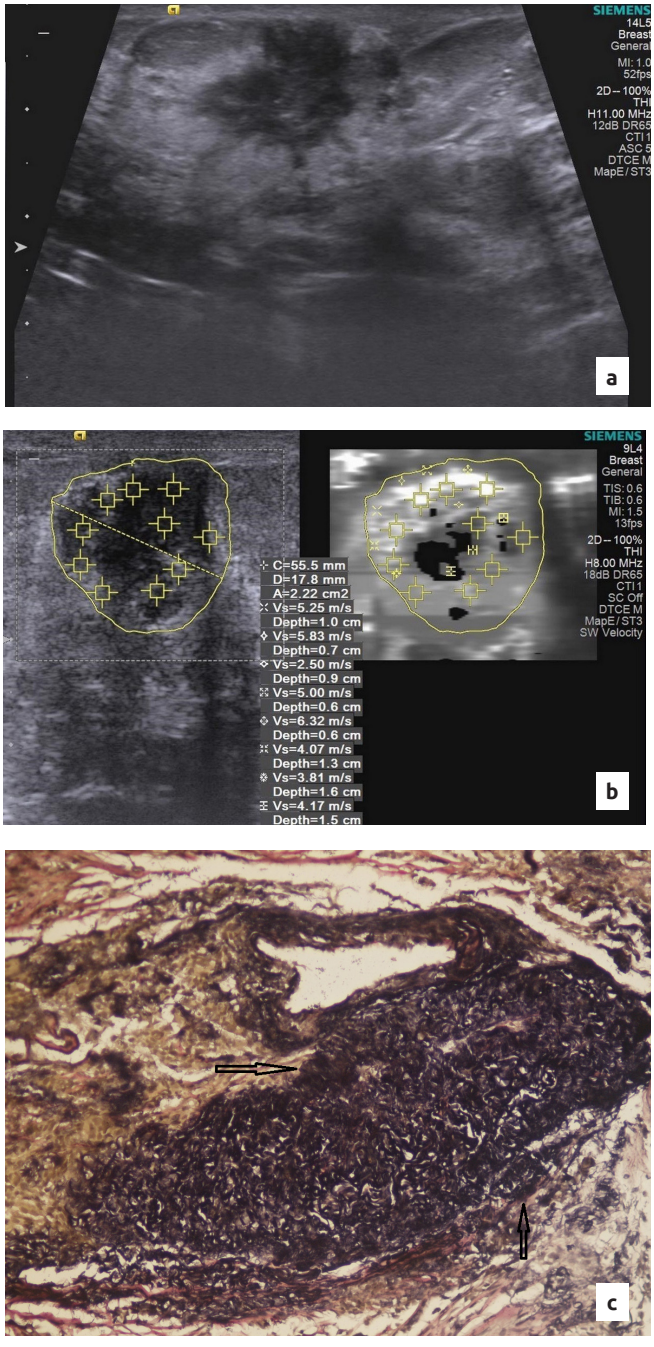

Figure 1. A 47-year-old patient with breast cancer. ARFI elastography of the lesion and elastic fiber appearance. **a)** BI-RADS 5 lesion on B-mode US, in non-parallel orientation, with irregular shape, and with a spicular margin feature. **b)** ARFI elastography imaging, showing high stiffness (mean SWV: 4.6 m/s). **c)** Elastin fiber dye (×200), elastin fiber areas in the form of large solid foci (red), which were distributed around tumor cell islands (up and right arrows). This was scored 3 according to the amount of elastic fibers.

ARFI: acoustic radiation force impulse; BI-RADS: Breast Imaging Reporting and Data System; US: Ultrasonography; SWV: shear wave velocity

In some studies, investigating elastin in breast cancer, elastin content was found to be correlated with low-grade breast cancer, estrogen receptor, negative human epidermal growth factor receptor 2 (HER-2), and low Ki-67 scores (20). In our study, low-grade cancers also showed high elastin fiber scores. Hence, elastin may be associated

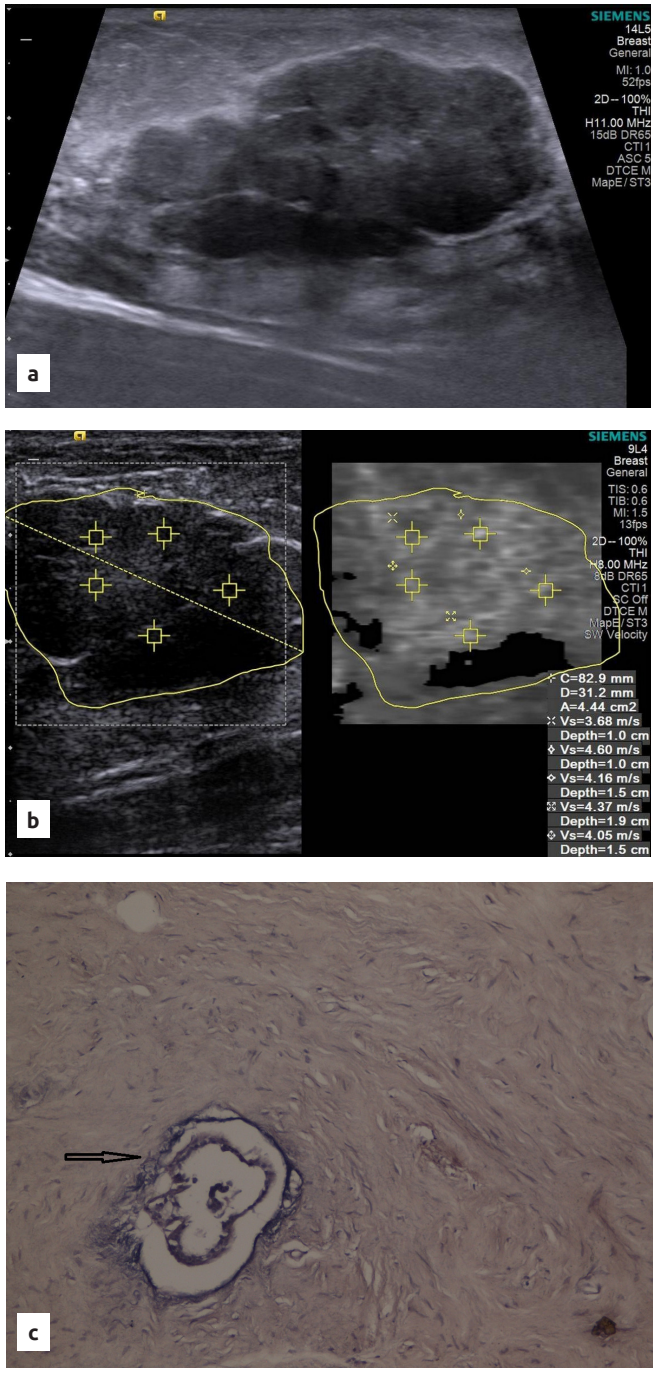

Figure 2. A 22-year-old patient. ARFI elastography and elastin fiber appearance of the lesion, which was pathologically confirmed as fibroadenoma. **a)** BI-RADS 4A lesion on B-mode US, in parallel orientation, with oval shape and lobular margin. **b)** ARFI elastography imaging, showing high stiffness (mean SWV: 4.1 m/s). **c)** Elastin fiber dye (×200). Thin, sparse elastin fibers (red), which were distributed around the ductus and stroma (right arrow). This was scored 1 according to the amount of elastin fibers.

ARFI: acoustic radiation force impulse; BI-RADS: Breast Imaging Reporting and Data System; US: Ultrasonography; SWV: shear wave velocity

with a better prognosis in invasive breast cancer. In our study, the absence of a relationship between elastin fiber score and breast cancer SWV values indicated that elastin fibers do not appear to contribute to tissue stiffness, and this supports the hypothesis that other ECM proteins are related to malignant lesion stiffness. In addition, the absence of correlation between tumor size and lymph node status with elastin fiber score is consistent with other studies in the literature (20). However, Chen et al. (20) found that tumor size and frequency of lymph node involvement were somewhat increased in interval tumors compared with for cancers detected by screening, and that interval tumors altogether lacked elastosis compared to those detected by screening. Therefore, the absence of elastosis has been associated with a poor prognosis.

Mera and Davies (21) showed that benign breast lesions had a significantly smaller average amount of elastin fiber than malignant lesions, implicating the elastin fiber content in the progression of breast carcinoma. Liu et al. (11) reported that the average collagen and elastin fiber areas were correlated with the maximum elasticity of breast lesions and that malignant lesions had higher collagen and elastin fiber contents than benign lesions. However, their work made no distinction concerning the extent to which collagen and elastin

Table 3. Correlation of elastin fiber scores with nodal status and tumor diameter of invasive cancer

Nodal status	Elastin fiber score		*p*-value
	Low elastin score (0–1)	High elastin score (2–3)	
N0, n (%)	0 (0.0)	7 (11.9)	0.49
N1, n (%)	7 (43)	33 (44)	
N2, n (%)	4 (25)	17 (22.7)	
N3, n (%)	5 (31)	18 (24.7)	
Tumor diameter			
T0, n (%)	0 (0.0)	0 (0.0)	0.89
T1, n (%)	6 (37.5)	24 (40.7)	
T2, n (%)	7 (43.8)	33 (55.9)	
T3, n (%)	3 (18.8)	2 (3.4)	
T4, n (%)	0 (0.0)	0 (0.0)	

n: number; N: node; T: tumor

Table 4. Comparison of elastin fiber scores and SWV of malignant breast lesions and fibroadenomas

Elastin fiber score	Invasive cancer		Fibroadenoma	
	Mean SWV (m/s) ± SD	*p*-value	Mean SWV (m/s) ± SD	*p*-value
Low elastin score (0–1)	5.571±1.9	0.175	4.23±1.5	0.02
High elastin score (2–3)	6.230±1.5		3.17±0.8	
Total	6.11±1.63		3.32±1.0	

SWV: shear wave velocity; SD: standard deviation

Table 5. The value of SWV and elastin fiber score of fibroadenomas according to lesions size

Fibroadenoma size	n (%)	Mean SWV (m/s) ± SD	p-value	Low elastin score (0–1), n (%)	High elastin score (2–3), n (%)	p-value
Diameter (<20 mm)	33 (35.9%)	2.87± 0.724	0.001	25 (24.2%)	8 (75.8%)	0.03
Diameter (≥20 mm)	59 (64.1%)	4.12 ± 0.96		54 (91.5%)	5 (8.5%)	

SWV: shear wave velocity; SD: standard deviation; n: number

contribute to flexibility (11). The fact that soft fibroadenomas in our study had more elastin fibers than harder adenomas may indicate that elastin supports flexibility in the tissues. However, Shi et al. (5) showed that the shape and aggregation of the fibers, as well as the amount of ECM components, were related to the stiffness of breast lesions. In our study, the amount of elastin fibers was taken into consideration, and no assessment of the arrangement of elastin fibers was made.

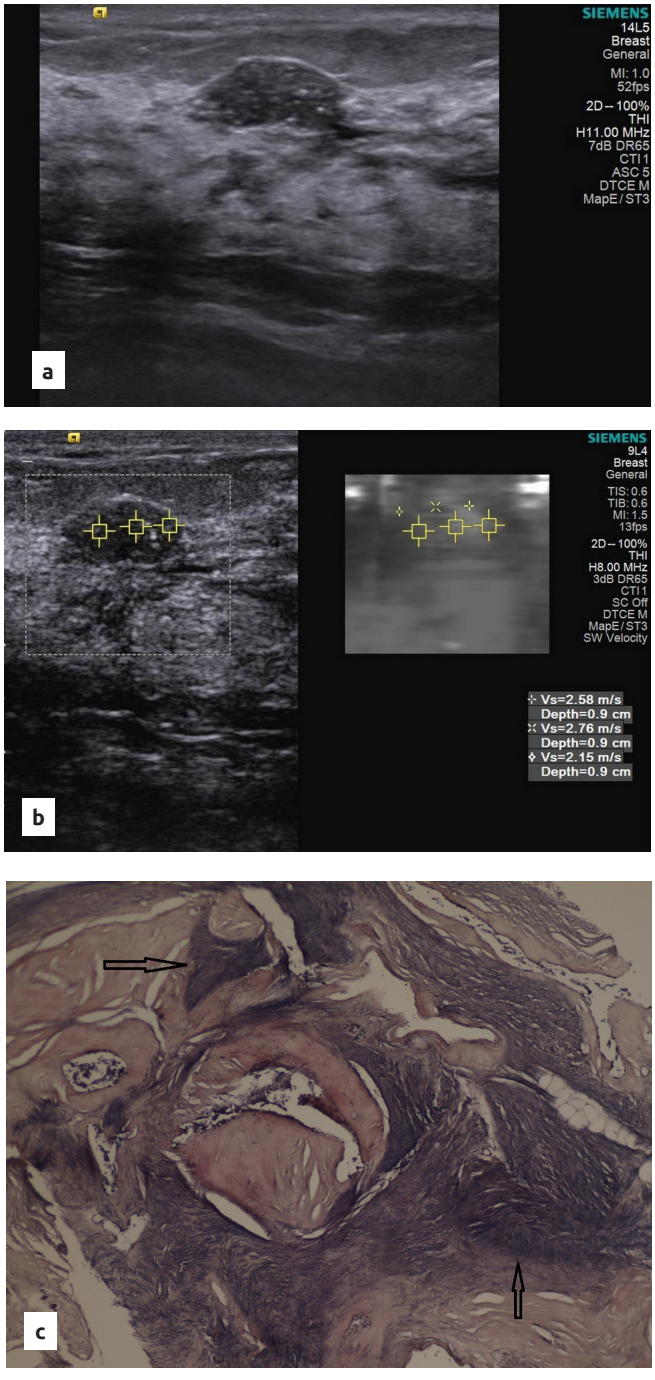

Figure 3. A 35-year-old patient. ARFI elastography and elastin fiber appearance of the lesion, which was pathologically confirmed as fibroadenoma. **a)** BI-RADS 4C lesion on B-mode US, in parallel orientation, with oval shape and a minimally irregular and angular margin. Foci of microcalcification are observed within the lesion. **b)** ARFI elastography imaging, showing low stiffness (mean SWV: 2.5 m/s). **c)** Elastin fiber dye (×100). Large foci of elastin fibers (red), which were distributed in the mesenchyme (up and right arrows). This was scored 3 according to the amount of elastin fibers.

ARFI: acoustic radiation force impulse; BI-RADS: Breast Imaging Reporting and Data System; US: ultrasonography; SWV: shear wave velocity

The amount of elastin fibers in fibroadenomas is reportedly slightly less than in breast carcinomas (22-24). In benign breast lesions, especially in sclerosing adenosis, myoepithelial cell proliferation suggests that the myoepithelium plays a role in elastin fiber synthesis (9). Elasbali et al. (25) detected elastin fibers in areas of fibrocystic change and fibroadenoma-like lesions.

The present study found that the harder and larger fibroadenomas contained fewer elastin fibers. Moreover, large fibroadenomas were found to have a harder structure, which is consistent with the literature (26). So, this finding suggests that, as fibroadenomas increase in size, elastin fibers in the stroma are replaced by other proteins present in the ECM. Lee et al. (27) showed that the hardness of fibroadenomas measured by elastography was associated with hyaline degeneration. The increase in fibroadenoma stiffness with age may be related to a low elastin fiber score, suggesting that the amount of the other stromal components in lesions increases with age.

There are a number of limitations of this study. The most important limitation of our study was that the correlation of elastin fiber score with other ECM proteoglycans, such as collagen, laminin, and fibronectin was not evaluated. In addition, no assessment was made of the arrangement of the elastin fibers within the surrounding tissues, which will affect the ability of these long, linear proteins to function as normal. More extensive studies should be conducted to investigate other ECM components in malignant lesions and their relationship to the prognosis and radiological appearance of malignant lesions. As only core biopsy samples were tested for elastin in this study, there could be potential sampling error. More accurate results may be obtained by studying excisional biopsy samples. In our study, the amount of elastic fibers in fibroadenoma subtypes was not examined separately and therefore does not provide information about the elastic fiber content of different histological types of fibroadenomas. A number of fibroadenoma variants are known, including juvenile, giant, complex, myxoid, cellular, and hyalinized fibroadenomas (28). Since these variants have different clinical behaviors, the potential for malignant transformation, and treatment strategies, the diagnosis of specific variants is important. With more specific future studies in this area, it will be possible to know the elastin fiber behavior in the ECM structure of fibroadenomas, especially complex fibroadenomas that are known to have a 3.1-fold increase in elastin content compared with the other fibroadenomas (29). This would provide more information about the optimal diagnostic and therapeutic approaches for all fibroadenomas. In our study, only quantitative SWV measurements were used during elastography. The lack of qualitative SWE evaluation is another limitation.

In conclusion, the relationship between elastin fiber score in fibroadenomas and malignant lesions was investigated. Low-grade breast cancers were associated with high elastin fiber scores, so elastin may be a prognostic marker for breast cancer. In addition, there was an inverse correlation between SWV values and the elastin fiber score in fibroadenomas, and thus variable elastin fiber content in this heterogeneous group of fibroadenomas might explain why SWV values of fibroadenomas are very variable. Finally, it may be possible to use, an elastin fiber score for differentiating fibroadenomas from malignancy but further studies are needed to make this accurate.

Ethics Committee Approval: The study was approved by Van Yüzüncü Yıl University Ethics Committee (decision number: 2020/03-09, date: 22/05/2020).

Informed Consent: Patient consent was waived due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.T.; Design: A.Y.; Supervision: İ.A., A.Y.; Data Collection and/or Processing: İ.A., O.T., A.Y.; Analysis and/or Interpretation: A.M.G.; Literature Search: O.T., A.M.G.; Writing: N.T.; Critical Review: N.T.

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

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

References

1. Kristensen JH, Karsdal MA. Elastin. In: Karsdal MA, editor. Biochemistry of Collagens, Laminins and Elastin.1st ed. Elsevier; 2016. pp. 197-202. [Crossref]
2. Oskarsson T. Extracellular matrix components in breast cancer progression and metastasis. Breast 2013; 22(Suppl 2): 66-72. (PMID: 24074795) [Crossref]
3. Acerbi I, Cassereau L, Dean I, Shi Q, Au A, Park C, et al. Human breast cancer invasion and aggression correlates with ECM stiffening and immune cell infiltration. Integr Biol (Camb) 2015; 7: 1120-1134. (PMID: 25959051) [Crossref]
4. Wang ZL, Sun L, Li Y, Li N. Relationship between elasticity and collagen fiber content in breast disease: a preliminary report. Ultrasonics 2015; 57: 44-49. (PMID: 25465961) [Crossref]
5. Shi XQ, Li J, Qian L, Xue X, Li J, Wan W. Correlation between elastic parameters and collagen fibre features in breast lesions. Clin Radiol 2018; 73: 595. (PMID: 29510833) [Crossref]
6. Xiao Y, Yu Y, Niu L, Qian M, Deng Z, Qiu W, et al. Quantitative evaluation of peripheral tissue elasticity for ultrasound-detected breast lesions. Clin Radiol 2016; 71: 896-904. (PMID: 27349474) [Crossref]
7. Kadar A, Tőkés AM, Kulka J, Robert L. Extracellular matrix components in breast carcinomas. Semin Cancer Biol 2002; 12: 243-257. (PMID: 12083854) [Crossref]
8. Martinez-Hernandez A, Francis DJ, Silverberg SG. Elastosis and other stromal reactions in benign and malignant breast tissue: an ultrastructural study. Cancer 1977; 40: 600-606. (PMID: 196733) [Crossref]
9. Davies JD, Barnard K, Young EW. Immunoreactive elastin in benign breast tissues. An immunoperoxidase study. Virchows Arch A Pathol Anat Histopathol 1982; 398: 109-117. (PMID: 6819699) [Crossref]
10. Lee SH, Moon WK, Cho N, Chang JM, Moon HG, Han W, et al. Shear-wave elastographic features of breast cancers: comparison with mechanical elasticity and histopathologic characteristics. Invest Radiol 2014; 49: 147-155. (PMID: 24169069) [Crossref]
11. Liu G, Zhang MK, He Y, Li XR, Wang ZL. Shear wave elasticity of breast lesions: would it be correlated with the extracellular matrix components? Gland Surg 2019; 8: 399-406. (PMID: 31538065) [Crossref]
12. American College of Radiology. ACR BI-RADS-US. In: ACR breast imaging reporting and data system. Reston: American College of Radiology; 2013.
13. Douglas JG, Shivas AA. The origins of elastica in breast carcinoma. J R Coll Surg Edinb 1974; 19: 89-93. (PMID: 4824318) [Crossref]
14. Bloom HJ, Richarson WW. Histologic grading and prognosis in breast cancer; A study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer 1957; 11: 359-377. (PMID: 13499785) [Crossref]
15. Ghosh L, Ghosh BC, Das Gupta TK. Ultrastructural study of stroma in human mammary carcinoma. Am J Surg 1980; 139: 229-232. (PMID: 6243882) [Crossref]
16. Jalkanen S, Salmi M. Cell surface monoamine oxidases: enzymes in search of a function. Embo J 2001; 20: 3893-3901. (PMID: 11483492) [Crossref]
17. Chamming's F, Latorre-Ossa H, Le Frère-Belda MA, Fitoussi V, Quibel T, Assayag F, et al. Shear wave elastography of tumour growth in a human breast cancer model with pathological correlation. Eur Radiol 2013; 23: 2079-2086. (PMID: 23553589) [Crossref]
18. Parfrey NA, Doyle CT. Elastosis in benign and malignant breast disease. Hum Pathol 1985; 16: 674-676. (PMID: 2989149) [Crossref]
19. Azzopardi JG. Elastosis and other connective tissue changes. In: W. B. Saunders, editor. Problems in Breast Pathology. 1st ed. London: 1976. p. 379-394.
20. Chen Y, Klingen TA, Wik E, Aas H, Vigeland E, Liestøl K, et al. Breast cancer stromal elastosis is associated with mammography screening detection, low Ki 67 expression and favourable prognosis in a population-based study. Diagn Pathol 2014 ;9: 230. (PMID: 25522915) [Crossref]
21. Mera SL, Davies JD. Elastosis in breast carcinoma: I. Immunohistochemical characterization of elastic fibres. J Pathol 1987; 151: 103-110. (PMID: 3033189) [Crossref]
22. Isaacson C, Greeff H, Murray JF, Posen J, Schmaman A. Elastosis in malignant tumours. S Afr Med J 1985; 68: 30-32. (PMID: 2990055) [Crossref]
23. Ushiki T. Collagen Fibers, Reticular Fibers and Elastic Fibers. A Comprehensive Understanding from a Morphological Viewpoint. Arch Histol Cytol 2002; 65: 109-126. (PMID: 12164335) [Crossref]
24. Zakout YM, Abdullah SM, Ali MA. Assessment of Elastosis in Invasive Ductal Carcinoma of the Breast Compared to Fibroadenoma among Sudanese Patients Using Conventional Histochemical Methods. Biotech Histochem 2012; 87: 122-225. (PMID: 21375429) [Crossref]
25. Elasbali AM, Onzi ZA, Hamza A, Khalafalla E, Ahmed HG. Morphological Patterns of Elastic and Reticulum Fibers in Breast Lesions. Health 2018; 10: 1625-1633. [Crossref]
26. Elseedawy M, Whelehan P, Vinnicombe S, Thomson K, Evans A. Factors influencing the stiffness of fibroadenomas at shear wave elastography. Clin Radiol 2016; 71: 92-95. (PMID: 26654133) [Crossref]
27. Lee KH, Kim SJ, Park YM, Kim W, Yoon JH, Song JW, et al. Gray-scale and color Doppler sonographic features of complex fibroadenomas of the breast. J Clin Ultrasound 2015; 43: 556-662. (PMID: 26200475) [Crossref]
28. Humphrey PA, Dehner LP, Pfeifer JD, editors. The Washington Manual of Surgical Pathology. 1st ed. Lippincott Williams & Wilkins; 2008.
29. Dupont WD, Page DL, Parl FF, Vnencak-Jones CL, Plummer WD Jr, Rados MS, et al. Long-term risk of breast cancer in women with fibroadenoma. N Engl J Med 1994; 331: 10-15. (PMID: 8202095) [Crossref]

Original Article

Eur J Breast Health 2022; 18(2): 141-147
DOI: 10.4274/ejbh.galenos.2022.2021-10-4

Overexpression of miR-490-5p/miR-490-3p Potentially Induces IL-17-Producing T Cells in Patients With Breast Cancer

Farhad Seif[1,2], Hajar Vaseghi[3], Mehdi Ariana[4], Shahla Mohammad Ganji[5], Mohammad Nazari[3], Kowsar Kiani Rad[6], Majid Pornour[3]

[1]Department of Immunology and Allergy, Academic Center for Education, Culture, and Research (ACECR), Tehran, Iran
[2]Neuroscience Research Center, Iran University of Medical Sciences, Tehran, Iran
[3]Department of Photo Healing and Regeneration, Medical Laser Research Center, Yara Institute, Academic Center for Education, Culture, and Research (ACECR), Tehran, Iran
[4]Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5]National Institute of Genetic Engineering and Biotechnology (NIGEB), Tehran, Iran
[6]Department of Genetic, Science Faculty, Shahrekord University of Medical Sciences, Shahrekord, Iran

ABSTRACT

Objective: Breast cancer (BC) is the most prevalent female cancer globally and this is also true in Iranian women. Alteration in circulating microRNAs affects the fate of immune cells, affecting immunological response to neoplasia.

Materials and Methods: We investigated the expression of *miR-490-5p* and *miR-490-3p* in peripheral blood mononuclear cells (PBMCs) and plasma of patients with BC. Moreover, the correlation of these microRNAs with the expression levels of *CD3d*, *interleukin 2 (IL-2), IL-2 receptor chain alpha (IL-2RA), forkhead box O1 (FOXO1)* and *nuclear factor of activated T cells 5 (NFAT5)* were investigated.

Results: Two groups, including 42 patients with BC, aged 22–75 years with stage I, II, III disease without administration of immunosuppressive chemotherapy regimens/radiotherapy and 40 healthy controls aged 27–70 years, participated. Overexpression and higher circulation levels of *miR-490-5p* and *miR-490-3p* were found in the patients with consequent down-regulation of all targets investigated in PBMCs. Furthermore, there was a significant negative correlation between the overexpression of these microRNAs and a reduction in levels of *CD3d*, *IL-2,* and *IL-2RA* in patients with BC.

Conclusion: These results suggest that down-regulation of the target genes by miR-490 may predispose and facilitate the production of Th17 lymphocytes and IL-17-producing Tregs. The variation in miR-490-5p/-3p and the investigated targets in the PBMCs of BC patients may be used as non-invasive diagnostic markers.

Keywords: miR-490; breast cancer; CD3d; FOXO1; IL-2; IL-2RA; NFAT5

Cite this article as: Seif F, Vaseghi H, Ariana M, Ganji SM, Nazari M, Rad KK, Pornour M. Overexpression of miR-490-5p/miR-490-3p Potentially Induces IL-17-Producing T Cells in Patients With Breast Cancer. Eur J Breast Health 2022; 18(2): 141-147

Key Points

- Overexpression and higher circulation of miR-490-5p and miR-490-3p were found in patients with stages I-III breast cancer.
- Furthermore, the expression of the targets of these microRNAs, including *FOXO1, CD3d, NFAT5, IL-2,* and *IL-2RA* were decreased in PBMCs of patients with breast cancer.
- These findings suggest a shift in lymphocyte population towards the production of Th17, Tregs, and IL-17-producing Tregs.

Introduction

Breast cancer (BC) is the most prevalent cancer amongst women worldwide, including in the Iranian population. Epigenetic factors play a crucial role in the initiation and progression of BC (1). One of these epigenetic factors is characterized by the variability in microRNAs in both tumoral tissues and circulation. These changes in microRNAs may act directly or indirectly to increase cancer cell proliferation or modification of the tumor microenvironment toward favorable tumor requirements, and drug resistance (2). MicroRNAs (miRNAs) are short (18–23 nucleotide), non-coding RNAs that regulate various complementary mRNAs post-transcriptionally. Secretory components, especially

Corresponding Author:
Majid Pornour; ma.pornour@gmail.com

Received: 04.11.2021
Accepted: 05.02.2022
Available Online Date: 01.04.2022

exosomes and microvesicles, have an important role in circulating and shuttling these regulatory factors throughout the body (3, 4).

Several studies have shown the effects of onco-microRNAs on the production of immune suppressor cells, including regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), M2 type macrophages, etc. (5-8). Tregs are a subpopulation of T-lymphocytes that have been shown to play a role in BC (9). Soheilifar et al. (6) showed that shuttling or concomitant overexpression of some of these onco-microRNAs, such as miR-182-5p and miR-182-3p, can target some proteins such as nuclear factor of activated T cell (NFAT) proteins, the T-cell receptor/complementarity determining region 3 (TCR/CD3) complex, and the interleukin 2/interleukin 2 receptor A (IL-2/IL-2RA) pathway to induce Tregs. The same study demonstrated that concomitant targeting FOXP3 inducer transcription factor (Forkhead box O1; FOXO1), NFATs that inhibited FOXP3 transcription factor, activation of interleukin-6 (IL-6) signaling, and inhibition of IL-2 signaling by miR-182-5p/-3p could induce an increase in the population of Tregs, including $FOXP3^+$ IL-17-producing Tregs and $FOXP3^+$ Tregs in BC patients (6).

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway has a pivotal impact on modulation of immune cells (10, 11). Activation of IL-2/IL-2RA induces STAT5 phosphorylation and activation (12). STAT5 is a transcription factor that induces FOXP3 expression, in addition to other inducer transcription factors, such as FOXO1 (13). In contrast, activation of NFAT proteins can activate T cells and induce their differentiation toward Th1 and Th2 subpopulations as well as suppress FOXP3 expression and Treg formation (14). Furthermore, initiation of IL-6 signaling causes STAT3 phosphorylation and inhibition of FOXP3 expression, as well (15). Activation of different members of the NFAT family, such as NFATc1 and NFATc2, recruit NFSATc4 that play a pivotal role in the induction of IL-2 by activation of T cells and activation of TCR/CD3 complex signal transduction (16-18). The expression or shuttling of miR-182/miR-183-96 cluster to immune cells in a BC microenvironment inhibits IL-2 and IL-2RA expression by targeting various TCR/CD3–associated signal transduction proteins (6). Moreover, miR-182-3p and miR-183 can negatively affect IL-2 production via targeting NFATc4 but also by directly targeting IL-2RA to prevent IL-2/IL-2RA signaling initiation (16).

However, NFAT5, the other member of NFAT family, induces IL-2 pathway and enhances the IL-17 inducer genes (19). The data derived from Gene Expression Omnibus (GEO) used to identify some microRNAs such as miR-490, etc. were upregulated in tumor tissues and over circulated in sera of patients with BC (6). Yang et al. (20) showed that miR-490-3p could directly target FOXO1. Also, Yang et al. (21) showed that targeting miR-490-5p inhibits the suppressive function of Tregs. However, some studies showed that miR-490-5p and miR-490-3p had potential in the production of Tregs and their polarization to IL-17-producing cells. Also, they potentially target *CD3d, IL-2, IL-2RA, FOXO1,* and *NFAT5* (22). Considering the role of miR-490 in IL-17 producing T cells formation and their potential in targeting *FOXO1, CD3d, IL-2, IL-2RA*, and *NFAT5*, after identification of miR-490-5p and miR-490-3p, we aimed to investigate their expression in peripheral blood mononuclear cells (PBMCs) and the plasma of the patients with BC. Finally, we evaluated the correlation of miR-490-5p and miR-490-3p with the expression of *CD3d, IL-2, IL-2RA, FOXO1*, and *NFAT5*.

Materials and Methods

Patient Selection

The participants were as follows. The patient group consisted of 42 patients with BC, aged 22–75 years who were patients in stages I, II, III of the disease without administration of immunosuppressive chemotherapy regimens/radiotherapy. The control group comprised 40 healthy individuals aged 27–70 years who were referred to Shohada Hospital. Written informed consent was obtained from the participants before the study. Demographic characteristics of all participants, including age, and marriage status, and pathologic data were gathered using a questionnaire from the pathology department. Exclusion criteria were advanced and metastatic cancer, neoadjuvant, a significant clinical disorder, psychiatric drug use for the past 5 months.

5 mL peripheral blood was collected from all participants in tubes containing EDTA and centrifuged at 150 g at 4 °C for 2 min. Then, we separated plasma, and then an equal volume of phosphate-buffered saline (PBS) was added to each blood sample and diluted gently. Ficoll-Hypaque (Pharmacia, Uppsala, Sweden) density centrifugation was used to isolate the PBMCs and the buffy coat, that contained lymphocytes, was collected after centrifuging at 800 g at 4 °C for 15 min. This study was approved by the Ethics Committee of the Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran (ethics code: IR.SBMU.RETECH.REC.1397.562).

RNA Extraction and qRT-PCR

Total RNA and circulating RNA were extracted from extracted PBMCs and 1 mL of plasma using the RiboEx LS reagent (Geneall, South Korea). Then, cDNA was synthesized for evaluation of the *CD3d, IL-2, IL-2RA, FOXO1*, and *NFAT5* using a first-strand cDNA synthesis kit (Thermo Fisher Scientific) followed by PCR according to the manufacturer's protocol. To assess microRNAs' levels (RNA-derived from plasma), specific hairpin loop primers were used to synthesize cDNA of the microRNAs of interest. The expression and variation of microRNAs (miR-490-5p and miR-490-3p) and their targets were evaluated by SYBR Green master mix kit (Genaxxon kit, Germany) on a MIC qPCR instrument (BioMolecular Systems, Australia). The specific primers are listed in Table 1. Eventually, qRT-PCR-derived data were analyzed by the $2^{-\Delta\Delta CT}$ and $2^{-\Delta CT}$ methods. Beta actin and GAPDH were utilized as housekeeping genes for comparison of the expression of target genes and RNU6 was used as the housekeeping gene for comparison of microRNAs.

Statistical Analysis

R-Studio 1.0.136 software was used to generate the correlation heatmap between miR-490-5p and miR-490-3p with their potential targets. In the current study, $p<0.05$ was considered statistically significant. Finally, multivariate analyses were performed to show the relationship between microRNAs and the expression level of their targets in the PBMCs of patients with BC. Comparison was made using the demographic and clinical characteristics of patients and controls. Statistical comparison was performed using SPSS, version 18 (IBM Inc., Armonk, NY, USA). Relative changes of microRNAs and their target genes in PBMCs of the patients with BC were assessed using student's t-test. Also, receiver operator characteristic (ROC) curve analysis was performed for miR-490-5p and -3p besides their targets in PBMCs samples using SPSS, version 18 (IBM Inc., Armonk, NY, USA).

Table 1. The primer sequences used in the current study

Stem loops for cDNA synthesis of microRNAs		
490-5p	5′-GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGAC ACCCACCT -3′	
490-3p	5′-GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGAC CAGCATGG -3′	
RNU6	5′-GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACAAAAATAT-3′	
Primers for qRT- PCR		
	Forward	**Reverse**
miR-490-5p	5′-GTGCAGGGTCCGAGGT-3′	5′-ATATCCATGGATCTCCAGGTGG-3′
miR-490-3p	5′-GTGCAGGGTCCGAGGT-3′	5′-TACAACCTGGAGGACTCCATG-3′
RNU6	5′-CGCTTCACGAATTTGCGTGTC-3′	5′-CGCTTCGGCAGCACATATACT-3′
GAPDH	5′-CCGAGCCACATCGCACAG-3′	5′-GGCAACAATATCCACTTTACCAG-3′
β-actin	5′-AGACGCAGGATGGCATGGG-3′	5′-GAGACCTTCAACACCCCAGCC-3′
CD3d	5′-AAGTGAGCCCCTTCAAGATACC-3′	5′-TCTGAGAGCAGTGTTCCCAC-3′
NFAT5	5′-AACAACATGACACTGGCGGT-3′	5′-CTCGAAAAACCAATCTGGCACG-3′
IL-2	5′-AAGGCCACAGAACTGAAACATC-3′	5′-ATTGCTGATTAAGTCCCTGGGT-3′
IL-2RA	5′- GATGCCAAAAAGAGGCTGACG-3′	5′-CCACATCAGCAGGTATGAATCCA-3′
FOXO1	5′- GAGGGTTAGTGAGCAGGTTACAC-3′	5′- TGCTGCCAAGTCTGACGAAAG-3′

Results

Pathologic Results

Pathology examinations showed that 23.8, 52.38, and 23.8 percent of the patients, respectively, were related to stages of I, II, and III. Almost 73.8% of patients expressed estrogen receptor (ER), and 64.2% were progesterone receptor (PR)-positive. Also, 21.42% of patients were human epidermal growth factor receptor 2 (HER-2)-positive. P53 mutation has been observed in 11.9 percent of these patients. Comparison between BC patients and control groups showed that patient groups had more abortions (nine abortions) even though the control group had more pregnancies (44 pregnancies) and longer time of breastfeeding (Table 2). However, there is not too much difference between other criteria between the two groups. Moreover, 36 of 40 people (90%) in the control group were married, and 36 of 42 people (86.7%) of patients were married. Of 42 patients, 35 were non-menopause (83.3%), while 87.5% of the control group were non- menopause (35 of 40 people). Moreover, there are no significant differences between these two groups in terms of menstruation (year). The pathological and clinical characteristics of patients with BC are summarized in Table 2.

Circulating miR-490-5p and miR-490-3p Were Increased in Plasma From Patients with BC

There was little published data on the expression of miR-490-3p in the plasma of the patients with BC. Thus miR-490-5p and miR-490-3p were evaluated separately. Expression analysis derived from real-time PCR showed that only miR-490-5p was significantly raised in the plasma of the patients with BC, whereas miR-490-3p in BC patients did not differ from healthy controls (Figure 1a). It was observed that miR-490-5p was increased 4.95-fold in patients with BC compared to controls (p<0.01).

MiR-490-5p and miR-490-3p Were Increased in PBMCs of Patients with BC

Both miR-490-5p and miR-490-3p were upregulated in PBMCs from patients with BC, by 15.6 times (p<0.001) and 13.14 times (p<0.001), respectively, compared to controls (Figure 1b).

Expression of Target Genes for miR-490-5p and miR-490-3p Were Decreased in PBMCs of Patients with BC

The expression levels of immune modulatory genes identified in the meta-analysis were compared between patients with BC and controls. This analysis showed significant down-regulation of the following genes: *FOXO1* 2.21 times (p<0.01), *CD3d* 3.9 times (p<0.01), *NFAT5* 4.8 times (p<0.01), *IL-2* 3.3 times (p<0.05), and *IL-2RA* 4.35 times (p<0.01) (Figure 1c). Correlation analysis was performed to investigate the relationship between expression changes in miR-490-5p and miR-490-3p and their respective target genes in patients and controls. There was a negative correlation between miR-490-5p and *CD3d* (r = -0.658, p = 0.001) and *IL-2RA* (r = -0.670, p<0.001), whereas there was a strong correlation between miR-490-5p and miR-490-3p in PBMCs of BC patients (r = 0.823, p<0.001). There was also a negative correlation between miR-490-3p and *CD3d* (r = -0.698, p<0.001), *IL-2* (r = -0.462, p = 0.03), and *IL-2RA* (r = -0.725, p<0.001). Moreover, there were a significant association between reduced expression of *CD3d* and *FOXO1* (r = 0.41, p = 0.05) and *CD3d* and *IL-2RA* (r = 0.505, p = 0.014). A significant relationship was found between *FOXO1* suppression and *NFAT5* (r = 0.495, p = 0.016). Finally, the decrease in *IL-2* expression was correlated with the decrease in *IL-2RA* (r = 0.601, p = 0.002) (Figure 2a).

ROC curve analysis was used to investigate the sensitivity and specificity of miR-490-5p, miR-490-3p, *FOXO1, CD3d, NFAT5, IL-2,* and *IL-2RA* expression levels in PBMCs of patients with BC compared to controls. The area under the curve (AUC) values for discrimination

Table 2. Pathological and clinical characteristics of patients with breast cancer

Age at diagnosis	**(25–35)**			**(35–45)**			**(45–55)**			**(Up to 55)**		
	(n = 9)			**(n = 13)**			**(n =16)**			**(n = 2)**		
Marriage	**Married**						**Unmarried**					
	n = 36						n = 4					
First menstruation (year)	Mean (n=40)											
	13±1.43											
Menopause	**Menopause**						**Non-menopause**					
	(n = 7)						(n = 33)					
Pregnancy	(n=36)											
	Mean (2.3±1.4)											
Abortion	(n = 9)											
	Mean (1.42±0.6)											
Breastfeeding (month)	(n = 36)											
	Mean (36.24±3.3)											
Axillary lymph nodes	N+						N-					
Invasive carcinoma histology	**Invasive lobular carcinoma (ILC)**						**Invasive ductal carcinoma (IDC)**					
	(n = 4)						(n = 36)					
Tumor grade	**Grade I**						**Grade II**			**Grade III**		
	(n = 10)						(n = 22)			(n = 10)		
Stage	**IA**	**IB**	**IC**				**IIA**	**IIB**	**IIC**	**IIIA**	**IIIB**	**IIIC**
	(n = 2)	(n = 3)	(n = 4)				(n = 13)	(n = 7)	(n = 2)	(n = 6)	(n = 4)	(n = 0)
Receptor status	ER+						PR+			HER-2+		
Positive	(n = 31)						(n = 27)			(n = 9)		
Negative	(n = 11)						(n = 15)			(n = 33)		
Total	(n = 40)											

ER: estrogen receptor; PR: progesterone receptor; HER-2: human epidermal growth factor receptor 2; n: number

of BC patients from healthy individuals were 0.840 (p<0.001) for miR-490-5p and 0.747 (p = 0.009) for miR-490-3p, respectively (Figure 2b). In the case of miR-490-5p and -3p, 73.5% and 69.7% of the positive outcomes would be correctly identified by diagnostic tests as positive. Also, 22.6% and 36.4% of the negative would be incorrectly specified by diagnosis test as positive for miR-490-5p and -3p, respectively. Moreover, 71.4, 68.8, 63.5, 62.5 and 61.5 percent of the positive outcomes would be correctly identified by diagnostic tests as positive for *IL-2, IL-2RA, CD3d, NFAT5* and *FOXO1*, respectively. Also, 33.3, 34.2, 28.6, 45 and 45.7 percent of the negative would be incorrectly specified by diagnosis test as positive for *IL-2, IL-2RA, CD3d, NFAT5,* and *FOXO1*, respectively. Similarly, the AUCs for BC patients compared to controls for expression levels of *CD3d*, *IL-2*, and *IL-2RA* were 0.680 (p = 0.014), 0.739 (p = 0.009), and 0.732 (p = 0.012), respectively. No significant difference was observed for *NFAT5* (p = 0.088) and *FOXO1* (p = 0.076) expression (Figure 2c). When the expression levels of miR490-5p and miR-490-3p and their target genes were examined in relation to clinical characteristics of the patients, no significant relationship was found.

Discussion and Conclusion

Previously, microarray-derived meta-analytical findings demonstrated an increased level of several microRNAs in both tumor tissue and plasma of patients with BC. Also, the immunosuppressive roles of some of these microRNAs have been described (6). Modulation of proteins involved in TCR/CD3 complex, IL-2/IL-2RA interactions and some transcription factors, such as NFATs, may direct T cells towards different Treg phenotypes (6). Furthermore, a concomitant decrease in FOXO1 level and reduction of NFATs has been associated with the production of IL-17-producing Treg (6). FOXO1, a transcription factor, induces *FOXP3* expression as the main step in directing T cells toward T regs, stimulated by STAT5 activation through some cytokine-related signaling pathways, such as the IL2/IL-2RA pathway (12, 13). In contrast, NFATs suppress the expression of *FOXP3* and induce Th1 and Th2 activation in normal conditions, together with *IL-2* expression, which stabilizes their functions (14, 15).

Several microRNAs have been reported to promote T-cell phenotype change from Th1 and Th2 toward Tregs or FOXP3+IL-17-producing Tregs, including *miR-21, miR-182-5p, miR-182-3p, miR-183, miR-*

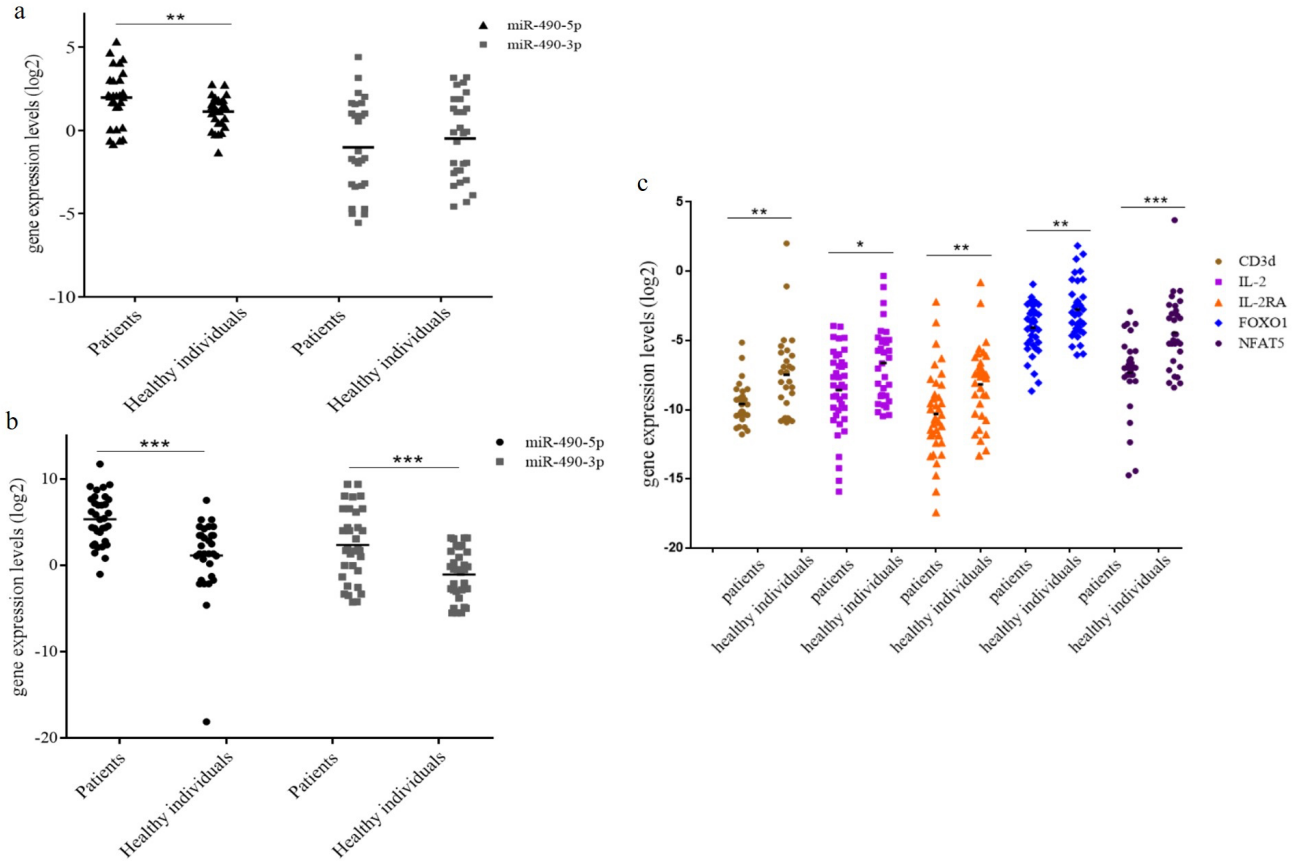

Figure 1. mir-490 cluster variation, circulation and possible effects in PBMC and plasma of BC patients. **a)** Variations of miR-490-5p and -3p in plasma of BC patients (derived from plasma data). **b)** Variations of miR-490-5p and miR-490-3p in PBMCs of patients with BC (derived from PBMC data), **c)** Variation of the miR-490-5p and -3p targets in PBMCs of patients with BC

BC: breast cancer; PBMCs: peripheral blood mononuclear cells

10a and Th17 cells are known to be involved in the progression of BC (5, 6, 23). Attenuation of TCR/CD3 signal transduction and reduction of NFATs, IL-2, and IL-2RA proteins may be effective in Treg production by activation of STAT5 (24). It has been shown that IL-2 expression is induced by NFATc1-4 and NFAT5 in different conditions (16-18, 25). However, Soheilifar et al. (6) showed that reduction of NFATs in patients with BC is associated with increased circulation of microRNAs, such as miR-182 and miR-183. Moreover, the negative effects of miR-490 on the expression of IL-2 have been confirmed by targeting NFAT5 (26).

The results of the current study showed a dramatic elevation of both miR-490-5p and miR-490-3p expression in PBMCs of BC patients, but only the plasma level of miR-490-5p was concomitantly increased while plasma levels of miR-490-3p were the same as in healthy controls. Therefore, increased expression of miR-490-5p in PBMCs and a concurrent high level in plasma means that these cells have both endogenous and exogenous sources of the microRNA whereas, because of the normal circulating levels of miR-490-3p, the only source potential pathogenic source for PBMCs is endogenous. Also, it was observed that the *CD3d* gene, coding for CD3d protein which is one of the CD3 complex proteins and a target for miR-490-3p, was significantly downregulated in PBMCs, and this reduction was associated with upregulation of miR-490-5p and miR-490-3p. So, both isoforms of miR-490-5p and miR-490-3p may be able to partially suppress the TCR/CD3 signal transduction cascade by downregulating *CD3d* expression, and may play a role in inhibition of T cell activation. In contrast, a significant reduction was observed in *IL-2RA* expression level. Moreover, this decrease in *IL-2RA* expression was associated with overexpression of both miR-490-5p and -3p isoforms. It is worth noting that a decrease in IL-2RA attenuates STAT5 phosphorylation and activation (12, 27). Such a decrease has been associated with increased levels of circulating onco-microRNAs, such as miR-182-3p, in sera of patients with BC (6). Furthermore, a significant reduction was found in *FOXO1* expression in the current study, which is targeted by miR-490-3p. This relationship, like other onco-microRNAs in BC, such as miR-182-3p, miR-183, has been confirmed in different studies (20, 28). However, simultaneous reduction of *FOXO1* and *NFAT* gene products may predispose to phenotype switch to IL-17-producing Tregs (6). Also, it has been shown that deficiency in the production of *FOXO1* has a key role in directing macrophages toward the M2-phenotype, which plays a critical role in the development of different kinds of cancers, especially BC (29).

It seems that miR-490 plays a role in decreased *IL-2* expression in PBMCs of patients with BC. Some studies have shown direct targeting by miR-490 of NFAT5, which induces IL-2 expression and production (5, 26). However, a significant reduction in *IL-2* expression level was

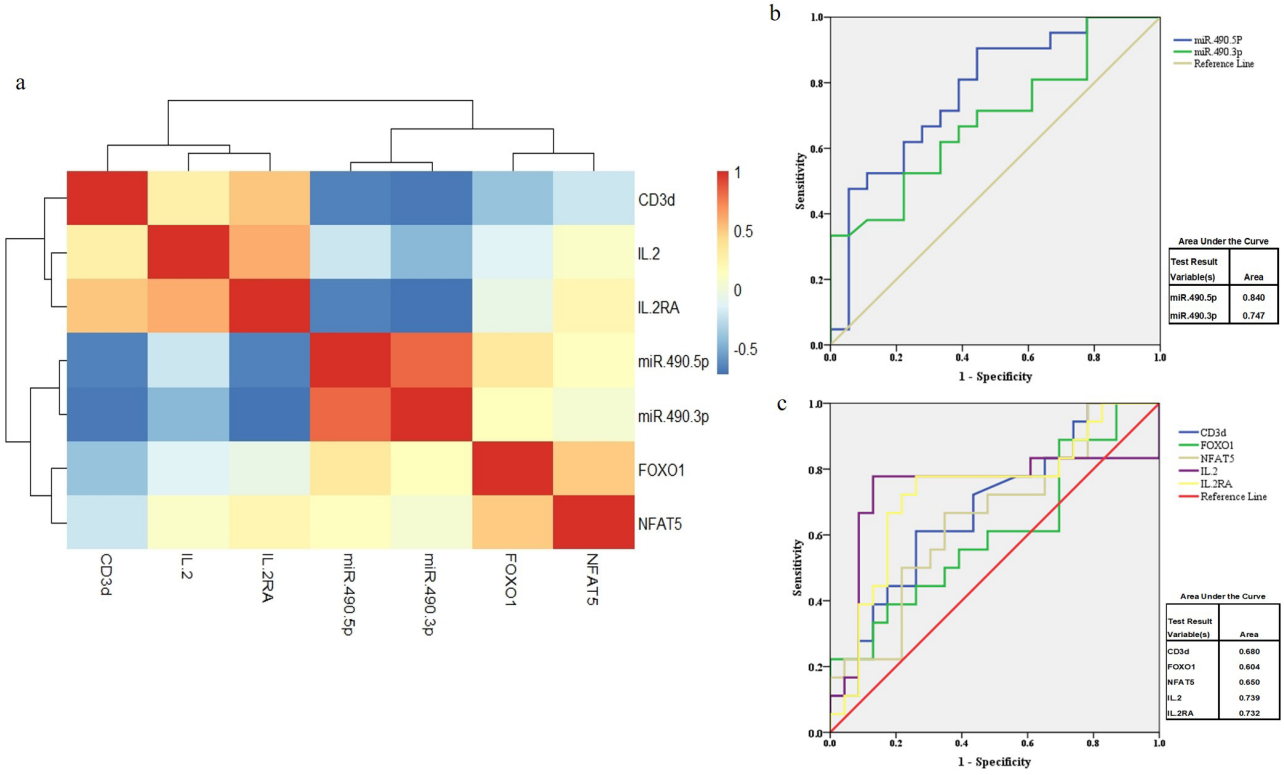

Figure 2. Hierarchical clustering analysis, Receiver operator characteristic (ROC) curve for mir-490 and area under the curves for target genes. **a)** Hierarchical clustering analysis showing the relationship between expression variability of miR-490-5p and miR-490-3p, *CD3d, NFAT5, IL-2, IL-2RA* and *FOXO1* in PBMCs of patients with BC, **b)** ROC curve was used for discrimination of BC patients. The areas under the curves are the gene expression level of *miR-490-5p*, *miR-490-3p* in PBMCs the patients with BC as compared with PBMCs of healthy individuals, **c)** The areas under the curves are the gene expression level of *CD3d*, *NFAT5*, *IL-2*, *IL-2RA*, and *FOXO1* in PBMCs of BC patients as compared with PBMCs of healthy individuals

BC: breast cancer; PBMCs: peripheral blood mononuclear cells

associated with miR-490-3p overexpression. Also, other studies have shown that *IL-2* was expressed irregularly in higher stages and in metastatic BC, and it is in line with our results in the case of IL-2 (30, 31). Thus, this study provides evidence that miR-490-5p and miR-490-3p may tip the balance between Treg and Th17 towards a Th17 T-cell phenotype through targeting *IL-2RA* as well as reduction of IL-2 by targeting *NFAT5*.

In conclusion, the results suggest potential for miR-490 to modulate the activity of *FOXO1, NFAT5, CD3d,* and *IL-2RA*. Over expression of mir-490-5p/-3p may facilitate the production of some phenotypes of T cells, which play a role in the progression of BC, including Th17, and IL-17-producing Tregs. A similar function has been suggested for other onco-microRNAs. Furthermore, the overexpression of both miR-490-5p and miR-490-3p and consequent suppression of their targets in PBMCs of BC patients may suggest a role as minimally invasive diagnostic markers in patients with BC.

Acknowledgements

We would like to thank Maryam Salari for her useful consultation regarding statistical analysis. This project was supported by grants 3008-10 and 11628 from the Academic Center for Education, Culture, and Research (ACECR) and the Cancer Research Center (CRC), respectively.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran with ethics number IR.SBMU.RETECH.REC.1397.562.

Informed Consent: Written informed consent was obtained from both groups prior to the initiation of the current study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A.; Concept: M.P.; Design: F.S., M.P.; Data Collection and/or Processing: H.V., S.M.G., M.N., K.K.R., M.P.; Analysis and/or Interpretation: H.V., S.M.G., M.N., M.P.; Literature Search: F.S., K.K.R., M.P.; Writing: F.S., M.P.

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

Financial Disclosure: Academic center for education, culture, and research (ACECR) and the Cancer Research Center (CRC), Grant/Award Number: 3008-10 and 11628, respectively.

References

1. Ariana M, Pornour M, Mehr SS, Vaseghi H, Ganji SM, Alivand MR, et al. Preventive effects of oxytocin and oxytocin receptor in breast cancer pathogenesis. Per Med 2018; 16: 25-34. (PMID: 30451597) [Crossref]

2. Torki Z, Ghavi D, Hashemi S, Rahmati Y, Rahmanpour D, Pornour M, et al. The related miRNAs involved in doxorubicin resistance or sensitivity of various cancers: an update. Cancer Chemother Pharmacol 2021; 88: 771-793. (PMID: 34510251) [Crossref]
3. Jafarzadeh N, Gholampour MA, Alivand MR, Kavousi S, Arzi L, Rad F, et al. CML derived exosomes promote tumor favorable functional performance in T cells. BMC cancer 2021; 21:1-1. (PMID: 34493241) [Crossref]
4. Heydarzadeh S, Ranjbar M, Karimi F, Seif F, Alivand MR. Overview of host miRNA properties and their association with epigenetics, long non-coding RNAs, and Xeno-infectious factors. Cell Biosci 2021; 11: 43. (PMID: 33632341) [Crossref]
5. Rodríguez-Galán A, Fernández-Messina L, Sánchez-Madrid F. Control of immunoregulatory molecules by miRNAs in T cell activation. Front Immunol 2018; 9: 2148. (PMID: 30319616) [Crossref]
6. Soheilifar MH, Vaseghi H, Seif F, Ariana M, Ghorbanifar S, Habibi N, et al. Concomitant overexpression of mir-182-5p and mir-182-3p raises the possibility of IL-17-producing Treg formation in breast cancer by targeting CD3d, ITK, FOXO1, and NFATs: A meta-analysis and experimental study. Cancer Sci 2021; 112: 589-603. (PMID: 33283362) [Crossref]
7. Hollen MK, Stortz JA, Darden D, Dirain ML, Nacionales DC, Hawkins RB, et al. Myeloid-derived suppressor cell function and epigenetic expression evolves over time after surgical sepsis. Crit Care 2019; 23: 355. (PMID: 31722736) [Crossref]
8. Julier Z, Park AJ, Briquez PS, Martino MM. Promoting tissue regeneration by modulating the immune system. Acta Biomater 2017; 53: 13-28. (PMID: 28119112) [Crossref]
9. Shevyrev D, Tereshchenko V. Treg heterogeneity, function, and homeostasis. Front Immunol 2020; 10: 3100. (PMID: 31993063) [Crossref]
10. Seif F, Khoshmirsafa M, Aazami H, Mohsenzadegan M, Sedighi G, Bahar M. The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells. Cell Commun Signal 2017; 15: 23. (PMID: 28637459) [Crossref]
11. Eslami N, Tavakol M, Mesdaghi M, Gharegozlou M, Casanova JL, Puel A, et al. A gain-of-function mutation of STAT1: a novel genetic factor contributing to chronic mucocutaneous candidiasis. Acta Microbiol Immunol Hung 2017; 64: 191-201. (PMID: 28597685) [Crossref]
12. Lin JX, Leonard WJ. The role of Stat5a and Stat5b in signaling by IL-2 family cytokines. Oncogene 2000; 19: 2566-2576. (PMID: 10851055) [Crossref]
13. Hedrick SM, Michelini RH, Doedens AL, Goldrath AW, Stone EL. FOXO transcription factors throughout T cell biology. Nat Rev Immunol 2012; 12: 649-661. (PMID: 22918467) [Crossref]
14. Lee W, Lee GR. Transcriptional regulation and development of regulatory T cells. Exp Mol Med 2018; 50: e456. (PMID: 29520112) [Crossref]
15. Maruyama T, Konkel JE, Zamarron BF, Chen W. The molecular mechanisms of Foxp3 gene regulation. Semin Immunol 2011; 23: 418-423. (PMID: 21752667) [Crossref]
16. Lee JU, Kim LK, Choi JM. Revisiting the concept of targeting NFAT to control T cell immunity and autoimmune diseases. Front Immunol 2018; 9: 2747. (PMID: 30538703) [Crossref]
17. Izsepi E, Himer L, Szilagyi O, Hajdu P, Panyi G, Laszlo G, et al. Membrane microdomain organization, calcium signal, and NFAT activation as an important axis in polarized Th cell function. Cytometry A 2013; 83: 185-196. (PMID: 23184643) [Crossref]
18. Rengarajan J, Tang B, Glimcher LH. NFATc2 and NFATc3 regulate T(H)2 differentiation and modulate TCR-responsiveness of naïve T(H) cells. Nat Immunol 2002; 3: 48-54. (PMID: 11740499) [Crossref]
19. Alberdi M, Iglesias M, Tejedor S, Merino R, López-Rodríguez C, Aramburu J. Context-dependent regulation of Th17-associated genes and IFNγ expression by the transcription factor NFAT5. Immunol Cell Biol 2017; 95: 56-67. (PMID: 27479742) [Crossref]
20. Yang X, Qu X, Meng X, Li M, Fan D, Fan T, et al. MiR-490-3p inhibits osteogenic differentiation in thoracic ligamentum flavum cells by targeting FOXO1. Int J Biol Sci 2018; 14: 1457-1465. (PMID: 30262997) [Crossref]
21. Yang L, Zhang C, Bai X, Xiao C, Dang E, Wang G. hsa_circ_0003738 Inhibits the Suppressive Function of Tregs by Targeting miR-562/IL-17A and miR-490-5p/IFN-γ Signaling Pathway. Mol Ther Nucleic Acids 2020; 21: 1111-1119. (PMID: 32871353) [Crossref]
22. Singh NP, Singh UP, Rouse M, Zhang J, Chatterjee S, Nagarkatti PS, et al. Dietary indoles suppress delayed-type hypersensitivity by inducing a switch from proinflammatory Th17 cells to anti-inflammatory regulatory T cells through regulation of microRNA. J Immunol 2016; 196: 1108-1122. (PMID: 26712945) [Crossref]
23. Kelada S, Sethupathy P, Okoye IS, Kistasis E, Czieso S, White SD, et al. miR-182 and miR-10a are key regulators of Treg specialisation and stability during Schistosome and Leishmania-associated inflammation. PLoS Pathog 2013; 9: e1003451. (PMID: 23825948) [Crossref]
24. Chinen T, Kannan AK, Levine AG, Fan X, Klein U, Zheng Y, et al. An essential role for the IL-2 receptor in T reg cell function. Nat Immunol 2016; 17: 1322-1333. (PMID: 27595233) [Crossref]
25. Aramburu J, López-Rodríguez C. Regulation of inflammatory functions of macrophages and T lymphocytes by NFAT5. Front Immunol 2019; 10: 535. (PMID: 30949179) [Crossref]
26. Griffiths R, Woods S, Cheng A, Wang P, Griffiths-Jones S, Ronshaugen M, et al. The transcription factor-microRnA Regulatory network during hESC-chondrogenesis. Sci Rep 2020; 10: 4744. (PMID: 32179818) [Crossref]
27. López-Rodríguez C, Aramburu J, Jin L, Rakeman AS, Michino M, Rao A. Bridging the NFAT and NF-kappaB families: NFAT5 dimerization regulates cytokine gene transcription in response to osmotic stress. Immunity 2001; 15: 47-58. (PMID: 11485737) [Crossref]
28. Kim KM, Park SJ, Jung SH, Kim EJ, Jogeswar G, Ajita J, et al. miR-182 is a negative regulator of osteoblast proliferation, differentiation, and skeletogenesis through targeting FoxO1. J Bone Miner Res 2012; 27: 1669-1679. (PMID: 2243139) [Crossref]
29. Yan K, Da TT, Bian ZH, He Y, Liu MC, Liu QZ, et al. Multi-omics analysis identifies FoxO1 as a regulator of macrophage function through metabolic reprogramming. Cell Death Dis 2020; 11: 800. (PMID: 32973162) [Crossref]
30. Kawaguchi K, Sakurai M, Yamamoto Y, Suzuki E, Tsuda M, Kataoka TR, et al. Alteration of specific cytokine expression patterns in patients with breast cancer. Sci Rep 2019; 9: 2924. (PMID: 30814616) [Crossref]
31. Dehqanzada ZA, Storrer CE, Hueman MT, Foley RJ, Harris KA, Jama YH, et al. Assessing serum cytokine profiles in breast cancer patients receiving a HER2/neu vaccine using Luminex technology. Oncol Rep 2007; 17: 687-694. (PMID: 17273752) [Crossref]

Original Article

Eur J Breast Health 2022; 18(2): 148-154
DOI: 10.4274/ejbh.galenos.2022.2021-9-2

The Comparative Frequency of Breast Cancer-Related Lymphedema Determined by Bioimpedance Spectroscopy and Circumferential Measurements

Pınar Borman[1], Ayşegül Yaman[2], Lütfi Doğan[3], Ayşe Arıkan Dönmez[4], Esra Gizem Koyuncu[5], Ayşegül Balcan[5], Sercan Aksoy[6], Cihangir Özaslan[3], Rabiye Akın[4], Kaniye Üneş[5]

[1]Department of Physical Medicine and Rehabilitation, Ankara City Hospital, University of Health Sciences Turkey, Ankara, Turkey
[2]Department of Physical Medicine and Rehabilitation, Gülhane Training and Research Hospital, University of Health Sciences Turkey, Ankara Turkey
[3]Department of Surgical Oncology, Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, University of Health Sciences Turkey, Ankara, Turkey
[4]Hacettepe University Faculty of Nursing, Ankara, Turkey
[5]Department of Physical Medicine and Rehabilitation, Hacettepe University Faculty of Medicine, Ankara, Turkey
[6]Department of Medical Oncology, Hacettepe University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Objective: The survival of patients with breast cancer has prolonged due to early diagnosis and modern methods of treatment and lymphedema has become the most important morbidity secondary to the treatment of the disease. Early detection and timely intervention have potential to reduce advanced breast cancer-related lymphedema. The aims of this study were to comparatively determine the frequency of subclinical/clinical lymphedema by using prospective monitoring with bioimpedance spectroscopy (BIS) and circumferential measurements in a group of patients who underwent breast cancer surgery.

Materials and Methods: Patients having breast cancer surgery were recruited between October 2018 and December 2019. Demographical and surgical properties were recorded. Extremity volumes by circumferential and BIS measurements were performed after surgery (baseline) and monitorizations were carried out at third and sixth months, in order to determine the frequency of subclinical/clinical lymphedema. L-Dex value of >6.5 was recently taken attention as subclinical lymphedema and values >7 were considered as clinical lymphedema. The presence of subclinical and clinic lymphedema was assessed by inter-limb volume difference (>5% and >10 respectively) based on the serial circumferential measurements in both affected and non-affected extremities. The functional status and quality of Life (QoL) were determined by quick-DASH and LYMQOL-Arm questionnaires respectively. The relationship between volume measurements, functional status and QoL scores were determined.

Results: Eighty-two female patients with a mean age of 49.6 years were included to the study. 30 (36.5%) and 21 (25.6%) of patients were determined as having subclinical/clinical lymphedema by BIS, while 18 (21.9%) and 19 (23.1%) of patients had subclinical/clinical lymphedema by circumferential-measurements at third-and-sixth months respectively. The functional and QoL scores were not correlated with circumferential volume measurements and BIS scores. There was a moderate-high correlation with BIS and circumferential measurements.

Conclusion: In conclusion 36.5% and 25.6% of our study group had subclinical and clinical lymphedema by BIS respectively during the 6 months surveillance period. Periodic monitoring of women with BIS allows early detection for lymphedema in more patients than in circumferential volume measurements, which may have implications for timely and necessary management.

Keywords: Bioempedance spectroscopy; breast cancer; circumferential volume measurement; lymphedema; quality-of-life; Turkish

Cite this article as: Borman P, Yaman A, Doğan L, Arıkan Dönmez A, Koyuncu EG, Balcan A, Aksoy S, Özaslan C, Akın R, Üneş K. The Comparative Frequency of Breast Cancer-Related Lymphedema Determined by Bioimpedance Spectroscopy and Circumferential Measurements. Eur J Breast Health 2022; 18(2): 148-154

Key Points

- Early detection of breast cancer-related lymphedema (BCRL) can prevent progression to its chronic stage eliminating morbidity and the need for more intensive costly treatments, and helps to reach the most successful outcomes in reducing the burden of disease.
- Herein we reported that periodic monitoring with the use of bioimpedance spectroscopy (BIS) allowed us to identify more patients with subclinical and/or clinical BCRL, compared to evaluation with circumferential volume measurements during the 6-month period.
- We suggest the implementation of BIS assessments into routine breast cancer follow-up programs in order to prevent and manage the potentially devastating effects of chronic BCRL, in patients with breast cancer surgery.

Corresponding Author:
Pınar Borman; pinarborman@gmail.com

Received: 09.09.2021
Accepted: 05.02.2022
Available Online Date: 01.04.2022

Introduction

Breast cancer is the most common cancer amongst women worldwide, with approximately two million cases each year. The incidence of breast cancer has been increased in recent decades, both in developed and developing countries (1). A report from Turkey reported that the incidence of breast cancer increased more than twice from 24/100,000 in 1993 to 50/100,000 in 2017 (2). In the same study the 5-year survival rate was found to be 86%. With improved surgical procedures and enhanced effectiveness of breast cancer treatment, the number of breast cancer survivors has increased dramatically and a significant number of women are dealing with the potential complications of treatment, including breast cancer-related lymphedema (BCRL) (1-3).

BCRL is a chronic, progressive condition characterized by accumulation of protein-rich fluid in the interstitial spaces due to disruption of the local lymphatic system after treatment with breast cancer surgery and/or radiation (3, 4). As lymphedema is under-recognized and under-documented, it is likely that the currently accepted rates of incidence and prevalence underestimate its magnitude (5, 6). Estimates of the risk of lymphedema after breast cancer treatment vary widely from 15%–94%, depending on differences in the extent and modality of therapies, discrepancies in diagnostic methods and duration of follow-up (4, 6, 7). Approximately 90% of the expected BCRL cases occur during the first 24 months after treatment (4, 8). Early or subclinical lymphedema can be objectively detected and serially assessed with appropriate surveillance methods but currently there is no consensus on the optimal screening regimen (8-11). Although a widely accepted methodological approach to the early diagnosis and/or surveillance of BCRL is lacking, bio-impedance spectroscopy (BIS) is perhaps the most commonly used approach for widespread clinical surveillance (8-14). Screening all patients for the development of BCRL has proven difficult, secondary to logistical and cost-related issues. Therefore, it may be useful to identify which patients are at highest risk of developing BCRL so that they can be targeted and enrolled in prospective surveillance programs. This would facilitate simple preemptive intervention, thereby reducing the development of irreversible, chronic BCRL (15-18).

Several studies and current guidelines have reported early detection and treatment of BCRL can prevent progression to its chronic stage, eliminating morbidity and the need for more intensive costly treatments (10, 17-19). Although there are numerous studies supporting the value of prospective surveillance with BIS compared to other methods, prospective studies with Turkish breast cancer patients are lacking (5, 20). Additional data about the frequency of lymphedema in this specific population may be useful to further validate the use of appropriate methods in BCRL screening programs.

The purpose of this study was to report the results of a 6-month surveillance program in order to determine the comparative frequency of subclinical and clinical BCRL, identified by BIS and circumferential volume measurements in a group of breast cancer patients.

Materials and Methods

Study Sample

Female patients who underwent breast cancer surgery in two different oncology centers (Hacettepe University Oncology Hospital and Abdurrahman Oncology Hospital), were enrolled to the study between October 2018 to December 2019. This prospective and descriptive study was approved by the local ethics committee and written informed consent was obtained from all participants. The study met the requirements of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the Hacettepe University (G0: 17/645).

Eligibility

The inclusion criteria were as follows: 1) aged between 18–65 years; and 2) having unilateral breast cancer surgery (breast conservation or mastectomy) with axillary lymph node dissection (ALND). Patients were excluded if they met the following criteria: 1) patients with history of contralateral breast cancer surgery; 2) previously documented diagnosis of BCRL; 3) having metal implants and/or pacemakers; 4) Patients having locoregional or distant metastases; 5) patients having musculoskeletal or venous disorders on the affected arm which may simulate or mask symptoms of lymphedema; 6) patients having renal and/or heart failure; 7) pregnancy; 8) immobile patients; and 9) patients with cognitive or neurological disorders. Chemotherapy and radiation therapy were allowed during the study.

Demographic and Clinical Data

Demographic and clinical properties including age, gender, Body Mass Index (BMI), marital status, and occupation were recorded. BMI was classified as normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese (≥30 kg/m^2) (21). Surgical characteristics, including type of breast surgery, either breast conserving therapy (BCT) or mastectomy, axillary surgery type including sentinel lymph node biopsy (SLNB) or ALND and stage of cancer [tumor, node, metastasis (TNM) staging 0–4] (22), and number of removed lymph nodes was collected from medical records. In addition therapeutic information was also collected including adjuvant chemotherapy, radiation therapy (axillary, breast/chest wall) and hormonal therapy.

Volume Measurements

Limb volume was measured using circumferential and BIS measurements (23-26). The baseline circumferential and BIS measurements were taken 3–6 weeks after the final breast cancer surgery in order to avoid misclassifying transient, post-operative swelling as BCRL. Then all patients underwent postoperative follow-up measurements at regular intervals of three months, during a 6-month period.

Circumferential Volume Measurements

For circumferential measurements, subjects sat straight on a chair with their arms relaxed by their sides and elbows straight. Both arms were measured at each test date. Circumferential measurements were performed using a standard 1-inch retractable tape, starting at the level of ulnar styloid, at 4 cm intervals along the arms and converted to an approximate arm volume to enable estimation of volume. Calculation of the limb segment volumes (millilitres-cm^3) was undertaken using a simplified truncated cone formula. Excess limb volume comparing affected and unaffected limbs and difference in excess volume (excess limb volume was expressed as a percentage of the unaffected limb volume, indicating how much larger the affected limb was compared to the unaffected limb) were calculated (23-25). The presence of subclinical and clinic lymphedema was assessed by inter-limb volume difference (>5% and >10% respectively) based on the serial circumferential measurements in both affected and non-affected extremities (25). Every patient was assessed by the same researcher.

BIS Measurements

BIS measurement was performed using an L-Dex U 400 device (Impedimed, Australia) and analyzed as previously described (26-28). Measurements were taken with patients in the supine position on a non-metallic surface, with their arms relaxed with palms facing down on a cushion. Electrodes were placed on each hand at the dorsal surface of the wrist between the process of the radial and the ulnar bones and on the dorsal surface of the hand, 1 cm proximal from the peak of the knuckle of the middle finger. A foot electrode was placed midway between the lateral and medial malleol processes on the ankle in the front of the foot (28). Two trained researchers performed all measurements.

The L-Dex ratio is the recommended metric when using BIS (13, 28, 29). The ratio of impedance at RO in the affected versus intact limb, adjusted for gender, upper limb and right left dominance, is expressed as the L-Dex ratio. An L-Dex ratio of -10 to +10 was considered normal. But L-Dex value of ≥6.5 was recently reported to indicate subclinical lymphedema and values ≥7 were considered to indicate clinical lymphedema (19).

Diagnosis of Lymphedema

Diagnosis of subclinical or clinical lymphedema is dependent on history, physical examination (3, 29, 30) and objective arm volume changes, which were assessed by arm circumferential measurements (23) and BIS given as an L-Dex value (19, 26).

Functional Status

Functional disability of the affected extremity was evaluated by the Turkish version of quick Disability of Arm, Shoulder and Hand questionnaire (Q-DASH). Q-DASH is a self-reported questionnaire evaluating symptoms and functional tasks associated with limitations of the arm, shoulder and hand. The validated Turkish version of Q-DASH contains 11 items and results in a score ranging from 0–100 with higher scores indicating more functional disability (31).

Quality of Life Assessment

Quality of Life (QoL) was assessed by the Turkish version of the Lymphedema Quality of Life Questionnaire-Arm (LYMQOL-Arm) (32). The LYMQOL-Arm was developed by Keeley et al. (33) to assess the impact of lymphedema of the arms on the QoL of the patients. It consists of four domains with 28 items. These domains are function, appearance, symptoms, and mood. The answers were evaluated on a four-point Likert scale (1 = not at all 2 = a little, 3 = quite a bit, 4 = a lot). Each item received a score between 1 and 4, with higher scores indicating a worse QoL. There is also an overall QoL rating. The 'overall QoL' item was scored 0–10. QoL and functional status assessments were performed by the same researcher.

At the first presentation of subclinical lymphedema, patients were provided with preventive methods. Preventive strategies included meticulous skin care, exercises and self-decongestive massage. In addition, they were prescribed over-the-counter compression garments. Patients with clinical lymphedema were referred to the lymphedema unit for complex decongestive therapy (CDT).

Statistical Analysis

Descriptive statistics were used to examine the frequency distributions and calculate the scores of scales and subscales, and defined using either mean ± standard deviation (SD), median and range or percentage values. Continuous variables were tested for normal distribution using the Shapiro-Wilk test. Student's t-test or Mann-Whitney U test were used as appropriate to compare differences in quantitative variables at different time points. The relationship between volume changes and QoL scores, functional status, as well as with clinical variables, was assessed using Pearson's correlation for parametric data and with Spearman's rho (correlation) for nonparametric data. All tests of statistical significance were two sided and considered statistically significant at $p<0.05$. Analyses were conducted using SPSS, version 21.0 (IBM Inc., Armonk, NY, USA).

Results

Between October 2018 and December 2019, a total of 134 females were screened among the patients who had breast cancer surgery. Of these 27 patients were excluded because of study eligibility criteria and seven patients did not agree to take part in the study. Therefore, the final study cohort size was 100 patients. Due to the unexpected coronavirus disease-2019 (COVID-19) pandemic, the sixth month follow-up measurements of 18 patients could not be performed and thus the data of 82 patients were reported.

The demographic and clinical characteristics of the patients are shown in Table 1. The mean age of the cohort was 49.6±10.42 years old (range: 27–65), and mean of BMI was 27.11 kg/m². A majority of participants were married, overweight/obese, and mostly housewives.

Concerning breast cancer treatment, the most common type of surgery was mastectomy followed by BCT. The majority of the patients had infiltrative ductal carcinoma. The median number of lymph nodes excised was 10 (min: 2–max: 28). The mean (median) time to measurement from surgery was 38 (29) days for all patients. Most of patients received chemotherapy and/or radiation therapy.

The difference in volumes and excess volumes, and L-Dex ratio, which were evaluated at baseline, three and six month follow-up are shown in Table 2. There were significant volume changes determined by circumferential measurements at all time points. Using circumferential measurements, 12 (14.6%) and 10 (12.2%) patients were diagnosed as subclinical lymphedema at the third and sixth month follow-ups, respectively. In regard to clinical lymphedema, 6 (7.3%) and 9 (10.9%) patients were identified at the third and sixth month follow-up respectively. The mean baseline L-Dex score was 2.15±7.69 (range: -14 to 17). Overall, 51 patients (62%) had an abnormal L-Dex score at some point during surveillance. Statistically significant changes during monitoring were observed in L-Dex ratios ($p<0.05$). Using L-Dex measurement, 19 (23.1%) and 7 (8.53%) subclinical lymphadema was diagnosed in the third and sixth-month follow-up respectively. In contrast, lymphedema based on an L-DEX ratio >10 was found in 11 (13.4%) and 14 (17.1%) patients at the third and sixth month follow-ups respectively. There was a moderate to high correlation between BIS and excess volume by circumferential measurements at both the third and sixth months ($r = 0.342^*$, $p = 0.011$, $r = 0.464^{**}$, $p<0.001$, respectively).

Functional status indicated by Q-DASH scores and the QoL scores are shown in Table 3. The mean values of Q-DASH scores tended to increase during follow-up but did not reach significance at any time point. No significant change in the mean scores of LYMQoL-subgroups was observed at the third and sixth month follow up. There was no correlation between volume measures by either by L-DEX or circumferential measurement and functional and QoL scores at the sixth month follow-up.

Table 1. The demographic and clinical variables of the patients

	(n = 82)
Age (years) mean (±SD)	49.60 (±10.42)
BMI (kg/m²) mean (±SD)	27.11 (±4.78)
Normal, n (%)	30 (36.6%)
Over-weight, n (%)	31 (37.8%)
Obese, n (%)	21 (25.6%)
Education	
Illiterate	1 (1.2%)
Primary school	31 (37.8%)
High school	23 (28%)
University	27 (32.9%)
Marital status	
Married	66 (80.5%)
Single	12 (14.6%)
Widow	4 (4.9%)
Occupation	
Housewife	38 (46.3%)
Officer	27 (32.9%)
Worker	4 (4.9%)
Retired	7 (8.5%)
Other	6 (7.3%)
Type of surgery	
BCT	30 (36.6%)
Mastectomy	52 (63.4%)
Axillary surgery	82 (100%)
SLNB	29
ALND	82
Breast cancer stage	
1	9 (11%)
2	49 (59.7%)
3	22 (26.8%)
4	2 (2.4%)
Histopathologic diagnosis	
Infiltrative ductal	58 (70.7%)
Infiltrative lobular	11 (13.4%)
Infiltrative mix type	3 (3.7%)
Others	10 (12.2%)
Adjunctive therapies	
Chemotherapy	60 (73.2%)
Radiation therapy	43 (52.4%)
Axillary	38 (46.3%)
Breast/chest wall	19 (23.2%)
Hormonal therapy	5 (6.1%)
None	10 (12.2%)
#excised lymph nodes	9.74 (± 6.87)

BMI: Body mass index; BCT: breast conserving therapy; SLNB: Sentinal lypmh node biopsy; ALND: Axillary lymph node dissection; SD: standard deviation; n: number

There was a positive correlation between the mean L-DEX ratio and excised lymph node number (r = 0.424, p = 0.001) and BMI (r = 0.324, p = 0.017).

The differences in clinical variables, excess volume and L-DEX ratio changes between patients with and without lymphedema are shown in Table 4. In regard to surgical factors, only the mean number of excised lymph nodes was significantly different in patients with and without lymphedema, indicating the impact of axillary node dissection on development of subclinical lymphedema. L-DEX ratio change and excess volume change during the six-month were different between the groups according to the presence of lymphedema, but did not reach significance.

The patients with a diagnosis of subclinical lymphedema were prescribed pressure garments and educated about self-management techniques, while the patients who were diagnosed with clinical lymphedema required CDT.

Discussion and Conclusion

The findings of this study demonstrated that prospective surveillance using BIS can detect subclinical and/or clinical BCRL more sensitively than circumferential volume measurements at the sixth month follow up. BIS identified 36.5% and 25.6% of patients with subclinical/clinical lymphedema at the third and sixth month of follow up, respectively, while 21.9% and 23.1% of patients had subclinical/clinical lymphedema by circumferential measurements at third and sixth months, respectively. However, there was a moderate to high correlation between BIS and circumferential measurements at 3 and 6-month follow-up. Furthermore, this study showed that the number of dissected lymph nodes was significantly associated with the development of lymphedema.

The number of breast cancer survivors is increasing globally and the likelihood of BCRL development as a consequence of breast cancer treatments is of worldwide significance (34). BCRL is a chronic, potentially devastating condition that may require long-term management and is associated with a risk of functional disability and psychosocial impact which may compromise the overall QoL. The optimal management of BCRL is based on early detection and timely intervention in order to prevent chronic and possibly irreversible complications and to reach most successful outcomes in reducing the burden of disease (3, 4, 10). During the earlier subclinical phase, the edema can easily be treated by education, self-massage and compression garments. However, when fibrosis is established more costly treatments, like manual lymphatic drainage multilayer bandaging, and pumps are needed and the lymphedema may not be reversible at advanced stages (10, 17). Current data support a surveillance approach and close monitoring of patients for the early diagnosis and treatment of BCRL in patients with breast cancer (4, 18, 35).

There is no gold standard for measuring sub-clinical lymphedema and it is difficult to know which measure is best for early detection. Current objective measures of BCRL include circumferential tape measurements, water displacement, BIS and perometry, which incorporate differences between limbs or from baseline (3, 7, 30). BIS is considered a reliable and sensitive measurement method which can predict the onset of lymphedema up to 10 months prior to clinically evident lymphedema and has been recommended to define subclinical lymphedema in previous studies (17-19, 26-28, 34). Early studies documented a conservative normal range between L-Dex scores >10

Table 2. The mean volume, excess volume and L-Dex ratio parameters of the patients at baseline and follow-ups

	Baseline	3 months	6 months	*p*-value
Volumes (cm^3) mean (± SD)	1960 (±426.5)	2075 (±463.9)	2086 (±462)	**<0.001**
Excess volume (%) mean (± SD)	4.05±2.47	7.73±5.54	8.62±6.19	**<0.001**
L-Dex ratio	2.15±7.69	7.11±13.99	10.71±14.02	**<0.001**

SD: standard deviation

Table 3. The functional and QoL scores in regard to follow-up periods

LYMQoL Scores	Baseline	3 months	6 months	*p*-value
Function	1.77±0.75	1.54±0.27	1.62±0.17	0.880
Appearance	1.54±0.74	1.20±0.33	1.26±0.28	0.881
Symptom	1.93±0.66	1.94±0.60	1.79±0.31	0.886
Mood	1.95±0.74	1.94±0.58	1.89±0.37	0.853
Overall	6.42±1.35	7.11±3.26	7.28±1.25	0.900
Q-DASH Score (mean ± SD)	38.54±20.88	37.29±19.06	39.81±13.42	0.104

p<0.001; Q-DASH: Quick Disability of Arm, Shoulder and Hand questionnaire; LYMQoL: Lymphedema Quality of life; SD: standard deviation

Table 4. The distribution of risk factors in regard to the presence of lymphedema

	Lymphedema (+)	Lymphedema (-)	*p*-value
Age (years)	48.56±10.55	47.39±9.2	0.686
BMI (kg/m^2)	26.82±4.57	24.50±5.22	0.092
Excised lymph node number (median)	14	8	**0.034***
Radiation therapy	50.1%	56.7%	0.875
L-Dex change (0^{th}–6^{th} month) (%)	13.82±15.44	5.07± 9.6	0.059
Excess volume change (0^{th}–6^{th} month) (%)	7.78 ±5.74	4.03± 3.28	0.062

Significant values are shown in bold.
*p<0.05; BMI: Body Mass Index

but more recently L-Dex score of >7 was considered as an indicator of subclinical lymphedema. (6, 8, 17, 19). Growing data support changing the cut-off point from >10 to >7 and thus improving the sensitivity for detecting subclinical BCRL (11, 18, 34), but few studies have used this cut-off point (19). Our study indicated a difference between comparative frequencies of subclinical/clinical lymphedema by BIS and circumferential volume measurements, supporting the use of this relatively new cut-off point.

Several studies have compared the estimated prevalence of lymphedema using different tools and diagnostic criteria. Previous studies highlighted L-DEX measurements as being more sensitive than circumferential measurements and other, subjective tools (11, 12, 19). One study with 176 women reported the prevalence with circumferential measurements as 0.6% but 11.9% with BIS (36). Kaufman et al. (11) reported 9.8% of patients with subclinical BCRL by BIS, whereas Keeley (18) reported lymphedema rate as 45.6% at 24 months. On the other hand, Soran et al. (34) reported the incidence of subclinical lymphedema to be as 33.8% with monitoring by BIS and only 4.4% were progressed to clinical lymphedema. Ridner et al. (19) compared BIS and circumference tape measurements to detect the magnitude of reduction in the rate of chronic BCRL with structured surveillance and found 17% of patients with clinical lymphedema. From Istanbul, Erdogan Iyigun et al. (20) found 21% of BCRL cases detected by BIS in their cross-sectional study, while Ozaslan and Kuru (5) reported the frequency of lymphedema to be 28% in 245 breast cancer patients. According to our data, overall subclinical and clinical lymphedema rates were 36.5% and 25.6% respectively by BIS measurements, which was higher than in previous studies, probably due to the use of the recently described lower cut-off points. In contrast to early studies from Turkey, we monitored the patients during the sixth months after treatment as a surveillance program and included assessment of functional status and QoL within the follow-up measurements.

Lymphedema impairs QoL, decreases physical functioning and affects psychosocial well-being (3, 24). Few studies have examined the relationship between clinical, functional and QoL variables and objective lymphedema measurements (36, 37). Lee et al. (36) explored the potential impact of the severity of lymphedema, determined by

L-Dex, on function and overall QoL in their patient group who had moderate to severe lymphedema. Higher L-Dex was related to poorer function but was not related to overall QOL of their limb lymphedema participants (36). In our study we could not find a relationship between volume changes, by either method assessed, and QoL or functional scores, which may be due to the subclinical and/or newly diagnosed and short-term lymphedema.

Prophylactic intervention could help to prevent and reduce BCRL but it may not be feasible to offer this approach to all patients who undergo breast cancer surgery. Implementing early interventions to only those who need it seems to be more logical and cost-effective. The risk factors for BCRL have previously been identified by several studies and highlighted in recent guidelines (3, 7, 15, 18, 24). Axillary radiation therapy, and BMI were found to increase the incidence of lymphedema (5, 24). The recent study by Erdogan Iyigun et al. (20) evaluated preoperative risk factors and found patient BMI, number of nodes involved and capsular invasion to be associated with preoperative BCRL. According to our results, the number of dissected lymph nodes was the most important factor for the development of subclinical lymphedema. The association of L-DEX scores with risk factors for BCRL was also consistent with previous data (18, 20, 27). Understanding the related factors can be an important strategy to improve postoperative status for high-risk patients, in order to avoid the need to screen all patients, which would be more costly and less efficient. Neither the baseline to six month change in L-Dex nor in excess volume was statistically different between the patients with and without lymphedema, a finding which could be due to the small group size with heterogeneous distribution of the significant variables.

Our study was limited by small sample size and relatively short follow-up, which may limit the power to detect differences and excludes any ability to comment concerning long-term outcomes. Due to the pandemic conditions, we could not complete the follow-up to the end of one year, but the study is ongoing. We plan to follow the patients for at least two years for better long-term data. Another limitation of our study was the lack of preoperative L-Dex data, which may limit definitive conclusions. However, the prospective design and implementation of L-DEX in the first month at initial consultation, as well as regular follow-up during a substantial period, add value to our data. Besides, our findings may add information about the national prevalence of subclinical BCRL in terms of surveillance method, as the first prospective study with a six month follow-up in this country.

In conclusion, regular periodic monitoring using BIS technology allowed the identification of more patients with subclinical and/or clinical BCRL compared to evaluation with circumferential volume measurements during the six month follow up period. This is further evidence to support prospective monitoring for lymphedema in patients with breast cancer. We suggest the implementation of BIS assessment into routine breast cancer follow-up programs in order to prevent and manage the potentially devastating effects of chronic BCRL, in patients after breast cancer surgery.

Acknowledgements: We thank Hacettepe University Scientific Research Project Coordination Unit for the funding of the Bioimpedance device (BAP-Project #16391).

Ethics Committee Approval: The study met the requirements of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the Hacettepe University (G0:17/645, date: 27.09.2017).

Informed Consent: This prospective and descriptive study was approved by the local ethics committee and written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: L.D., A.B., S.A., C.Ö.; Concept: P.B., E.G.K., C.Ö.; Design: P.B., S.A.; Data Collection and/or Processing: A.Y., A.A.D., E.G.K., S.A., R.A., K.Ü.; Analysis and/or Interpretation: A.Y., R.A.; Literature Search: A.Y., R.A.; Writing: P.B., A.A.D.

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

Financial Disclosure: This research received a grant from Hacettepe University Scientific Research Project Coordination Unit (2017/16391).

References

1. Torgbenu E, Luckett T, Buhagiar MA, Chang S, Phillips JL. Prevalence and incidence of cancer related lymphedema in low and middle-income countries: a systematic review and meta-analysis. BMC Cancer 2020; 209: 604. (PMID: 32600278) [Crossref]
2. Özmen V, Özmen T, Doğru V. Breast Cancer in Turkey; An Analysis of 20.000 Patients with Breast Cancer. Eur J Breast Health 2019; 15: 141-146. (PMID: 31312788) [Crossref]
3. McLaughlin SA, Staley AC, Vicini F, Thiruchelvam P, Hutchison NA, Mendez J, et al. Considerations for Clinicians in the Diagnosis, Prevention, and Treatment of Breast Cancer-Related Lymphedema: Recommendations from a Multidisciplinary Expert ASBrS Panel : Part 1: Definitions, Assessments, Education, and Future Directions. Ann Surg Oncol 2017; 24: 2818-2826. (PMID: 28766232) [Crossref]
4. Rockson SG. Lymphedema after breast cancer treatment. N Engl J Med 2018; 379: 1937-1944. (PMID: 30428297) [Crossref]
5. Ozaslan C, Kuru B. Lymphedema after treatment of breast cancer. Am J Surg 2004; 187: 69-72. (PMID: 14706589) [Crossref]
6. Levenhagen K, Davies C, Perdomo M, Ryans K, Gilchrist L. Diagnosis of upper quadrant lymphedema secondary to cancer: Clinical practice guideline from the oncology section of the American Therapy Association. Phys Ther 2017; 97: 729-745. (PMID: 28838217) [Crossref]
7. Dylke ES, Schembri GP, Bailey DL, Bailey E, Ward LC, Refshauge K, et al. Diagnosis of upper limb lymphedema development of an evidence-based approach. Acta Oncol 2016; 55: 1477-1483. (PMID: 27333213) [Crossref]
8. Bulley C, Gaal S, Coutts F, Blyth C, Jack W, Chetty U, et al. Comparison of breast-cancer-related lymphedema (upper limb swelling) prevalence estimated using objective and subjective criteria and relationship with quality of life. Biomed Res Int 2013; 2013: 807569. (PMID: 23853774) [Crossref]
9. Bundred NJ, Stockton C, Keeley V, Riches K, Ashcroft L, Evans A, et al. Compasiron of multi-frequency bioimpedance with perometry for the early detection and intervention of lympheoedema after axillary node clearance for breast cancer. Breast Cancer Res Treat 2015; 151: 121-129. (PMID: 25850535) [Crossref]
10. Heller DR, Killelea BK, Sanft T. Prevention is key: Importance of early recognition and referral in combating breast cancer-related lymphedema. J Oncol Pract 2019; 15: 263-265. (PMID: 31075214) [Crossref]
11. Kaufman DI, Shah C, Vicini FA, Rizzi M. Utiliation of bioimpedance spectroscopy in the prevention of chronic breast cancer-related lymphedema. Breast Cancer Res Treat 2017; 166: 809-815. (PMID: 28831632) [Crossref]
12. Coroneos CJ, Wong FC, DeSynder SM, Shaitelman SF, Schaverian MV. Correlation of L-Dex Bioimpedance spectroscopy with limb volume and

lymphatic function in lymphedema. Lymphat Res Biol 2019; 17: 301-307. (PMID: 30388062) [Crossref]

13. Seward C, Skolny M, Brunelle C, Asdourian M, Salama L, Taghian AG. A comprehensive review of bioimpedance spectroscopy as a diagnostic tool for the detection and measurement of breast cancer-related lymphedema. J Surg Oncol 2016; 114: 537-542. (PMID: 27393376) [Crossref]
14. Soran A, Menekşe E, Girgis M, DeGore L, Johnson R. Breast cancer-related lymphedema after axillary lymph node dissection: does early posteoperative prediction model work? Support Care Cancer 2016; 24: 1413-1419. (PMID: 26349574) [Crossref]
15. Vicini F, Shah C, Whitworth P, Walker M, Shi J. Correlation of bioimpedance spectroscopy with risk factors for the development of breast cancer-related lymphedema. Lymphat Res Biol 2018; 16: 533-537. (PMID: 30133336) [Crossref]
16. Whitworth PW, Cooper A. Reducing chronic breast cancer-related lymphedema utilizing a program of prospective surveillance with bioimpednace spectroscopy. Breast J 2018; 24: 62-65. (PMID: 29063664) [Crossref]
17. Gebruers N, Verbelen H, De Vrieze T, Vos L, Devoogdt N, Fias L, et al. Current and future perspectives on the evaluation, prevention and conservative management of breast cancer related lymphoedema: A best practice guideline. Eur J Obstet Gynecol Reprod Biol 2017; 216: 245-253. (PMID: 28811052) [Crossref]
18. Keeley V. The Early Detection of Breast Cancer Treatment-Related Lymphedema of the Arm. Lymphat Res Biol 2021; 19: 51-55. (PMID: 33270493) [Crossref]
19. Ridner SH, Dietrich MS, Spotanski K, Doersam JK, Cowher MS, Taback B, et al. A prospective study of L-Dex values in breast cancer patients pretreatment and through 12 months postoperatively. Lymphat Res Biol 2018; 16: 435-441. (PMID: 30130147) [Crossref]
20. Erdogan Iyigun Z, Selamoglu D, Alco G, Pilancı KN, Ordu C, Agacayak F, et al. Bioelectrical impedance for detecting and monitoring lymphedema in patients with breast cancer. Preliminary results of the flörence nightingale breast study group. Lymphat Res Biol 2015; 13: 40-45. (PMID: 25526543) [Crossref]
21. Purnell JQ. Definitions, Classification, and Epidemiology of Obesity. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al. editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. (PMID: 25905390) [Crossref]
22. Cserni G, Chmielik E, Cserni B, Tot T. The new TNM-based staging of breast cancer. Virchows Arch 2018; 472: 697-703. (PMID: 29380126) [Crossref]
23. De Vrieze T, Gebruers N, Tjalma WA, Nevelsteen I, Thomis S, De Groef A, et al. What is the best method to determine excessive arm volume in patients with breast cancer-related lyphoedema in clinical practice? Reliability, time efficiency and clinical feasibility of five different methods. Clin Rehabil 2019; 33: 1221-1232. (PMID: 30880473) [Crossref]
24. Executive Committee of the International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. Lymphology 2020; 53: 3-19. (PMID: 32521126) [Crossref]
25. Karges JR, Mark BE, Stikeleather SJ, Worrell TW. Concurrent validity of upper extremity volume estimation: Comparison of calculated volume derived from girth measurements and water displacement volume. Phys Ther 2003; 83: 134-145. (PMID: 12564949) [Crossref]
26. Laidley A, Anglin B. The Impact of L-Dex(®) Measurements in Assessing Breast Cancer-Related Lymphedema as Part of Routine Clinical Practice. Front Oncol 2016; 6: 192. (PMID: 27656420) [Crossref]
27. Vicini F, Shah C, Lyden M, Whitworth P. Bioelectrical impedance for detecting and monitoring patients for the development of upper limb lymphedema in the clinic. Clin Breast Cancer 2012; 12: 133-137. (PMID: 22444720) [Crossref]
28. Shah C, Vicini FA, Arthur D. Bioimpedance spectroscopy for breast cancer related lymphedema assessment: clinical practice guidelines. Breast J 2016; 22: 645-650. (PMID: 27487985) [Crossref]
29. Ward LC, Dylke E, Czerniec S, İsenring E, Kilbreath SL. Confirmation of the reference impedance ratios used for assessment of breast cancer-related lymphedema by bioelectrical impedance spectroscopy. Lymphat Res Biol 2011; 9: 47-51. (PMID: 21417767) [Crossref]
30. Greene AR, Goss JA. Diagnosis and staging of lymphedema. Semin Plast Surg 2018; 32: 12-16. (PMID: 29636648) [Crossref]
31. Koldas Dogan S, Ay S, Evcik D, Baser O. Adaptation of Turkish version of the questionnaire of the Quick disability of the arm, shoulder and hand (Quick DASH) in patients with carpal tunnel syndrome. Clin Rheumatol 2011; 30: 185-191. (PMID: 20411289) [Crossref]
32. Borman P, Yaman A, Denizli M, Karahan S, Özdemir O. The reliability and validity of Lymphedema Quality Of Life Questionnaire-Arm in Turkish patients with upper limb lymphedema related with breast cancer. Turk J Phys Med Rehabil 2018; 64: 205-212. (PMCID: PMC6657787) [Crossref]
33. Keeley V, Crooks S, Locke J, Veigas D, Riches K, Hilliam R. A quality of life measure for limb lymphoedema (LYMQOL). Journal of Lymphoedema 2010; 5: 26-37. [Crossref]
34. Soran A, Ozmen T, McGuire KP, Diego EJ, McAuliffe PF, Bonaventura M, et al. The importance of detection of subclinical lymphedema for the prevention of breast cancer-related clinical lymphedema after axillary lymph node dissection; a prospective observational study. Lymphat Res Biol 2014; 12: 289-294. (PMID: 25495384) [Crossref]
35. O'Toole J, Jammallo LS, Skolny MN, Miller CL, Elliott K, Specht MC, et al. Lymphedema following treatment for breast cancer: A new approach to an old problem. Crit Rev Oncol Hematol 2013; 88: 437-446. (PMID:23777977) [Crossref]
36. Lee TS, Morris CM, Czerniec SA, Mangion AJ. Does Lymphedema Severity Affect Quality of Life? Simple Question. Challenging Answers. Lymphat Res Biol 2018; 16: 85-91. (PMID: 28453410) [Crossref]
37. Lanza M, Bergmann A, Ferreira MG, de Aguiar SS, Dias Rde A, Abrahão Kde S, et al. Quality of Life and Volume Reduction in Women with Secondary Lymphoedema Related to Breast Cancer. Int J Breast Cancer 2015; 2015: 586827. (PMID: 26843988) [Crossref]

Original Article

Eur J Breast Health 2022; 18(2): 155-162
DOI: 10.4274/ejbh.galenos.2022.2021-12-2

Application of Personal Health Record in Enhancing the Quality of Life in Patients With Breast Cancer Who Received Adjuvant Hormonal Therapy

Fuka Takada[1], Hiromi Okuyama[1,2,3], Seigo Nakamura[3], Ken-ichi Fujita[1]

[1]Division of Cancer Genome and Pharmacotherapy, Department of Clinical Pharmacy, Showa University School of Pharmacy, Tokyo, Japan
[2]Department of Advanced Cancer Translational Research Institute, Showa University, Tokyo, Japan
[3]Division of Breast Surgical Oncology, Department of Surgery, Showa University School of Medicine, Tokyo, Japan

ABSTRACT

Objective: Recently, personal health records (PHR) have become a communication tool between patients and medical professionals. PHR applications (PHR app) can be installed on smartphones to record patient-reported outcomes (PROs). This study prospectively examined whether patients with breast cancer could record PROs, including subjective and objective symptoms, on PHR app.

Materials and Methods: Patients who received adjuvant hormonal therapy were enrolled. The patients were asked to collect PROs related to physical conditions, symptoms, and medications on their PHR app from the beginning of therapy for one month. Quality of life (QoL) was evaluated before treatment initiation and one month after. Patients completed a questionnaire of their opinions concerning the PHR app after use.

Results: Fourteen patients were enrolled between October and December 2020. All patients could use the PHR app during the study period without any negative effects on QoL. Eleven (79%) patients fully recorded their PROs on the app. Typical side effects induced by hormonal therapy to reduce the QoL were observed (hot flash in two patients, 14.3%). The questionnaire revealed that approximately 70% wanted to use the PHR app in the future to communicate with medical staff and to report adverse events. Specifically, 90% of patients who experienced difficulty communicating with medical staff wanted to use the PHR app. Some patients wanted to utilize the PHR app to set reminders to take medications.

Conclusion: The PHR app can be applied as a communication tool between patients taking adjuvant hormonal therapy and medical professionals.

Keywords: Breast cancer; quality of life; personal health records; hormonal therapy; patient reported outcome; adverse event

Cite this article as: Takada F, Okuyama H, Nakamura S, Fujita K. Application of Personal Health Record in Enhancing the Quality of Life in Patients With Breast Cancer Who Received Adjuvant Hormonal Therapy. Eur J Breast Health 2022; 18(2): 155-162

Key Points

- To appropriately manage the QoL of breast cancer patients who receive adjuvant hormonal therapy, it is important for medical professionals to know the physical conditions and/or symptoms, including adverse events (patient-reported outcomes, PROs), of patients.
- Personal health record application (PHR app) is an electronic note that can be installed on smartphones to record PROs.
- We prospectively examined whether patients could record their PROs on the PHR app.
- All patients could record PROs on the PHR app without affecting their QoL.
- Most of the patients, especially those who had difficulty communicating with medical staff, wanted to use the PHR app to share their adverse events with medical staff.

Introduction

Many clinical studies have demonstrated the efficacy of adjuvant hormonal therapy for patients with hormone receptor-positive breast cancer (1-3). Although hormonal therapy has demonstrable advantages in terms of lower recurrence rate and longer survival, many patients experience adverse events, such as menopausal symptoms including hot flashes, joint pain, and night sweats caused by the blockade of hormone receptors (4). These side effects induced by adjuvant hormonal therapy decrease the quality of life (QoL) of patients and occasionally cause early discontinuation of the treatment (5-7). It has been reported that patients should continue the adjuvant hormonal therapy for at least 5 years to

Corresponding Author:
Ken-ichi Fujita; k.fujita@med.showa-u.ac.jp

Received: 29.12.2021
Accepted: 07.02.2022
Available Online Date: 01.04.2022

prevent recurrence and/or death (8). Therefore, adequate management of adverse events induced by hormonal therapy is required.

In order to complete long-term adjuvant hormonal therapy without lowering the QoL of patients, physicians need to collect information on adverse events from patients and make appropriate treatment plans at the right time. However, patients are often reluctant to report menopausal symptoms to their physicians (9).

Recently, the importance of the management of adverse events occurring in patients, based on patient-reported outcomes (PROs), which are subjective patient evaluation of adverse events and/or QoL, has been recognized (10). In the United States, the use of web-based PRO reporting was demonstrated to improve the QoL of patients who received routine chemotherapy in the outpatient setting for advanced solid tumors (11). Clinicians and nurses were able to evaluate the symptoms of patients through PROs and give appropriate advice to the patients, which led to an improvement in their QoL.

The personal health record (PHR) is an electronic recorder that allows patients to record their physician's diagnoses, symptoms, and/or medications during therapy (12). Patients and their family members can share these lines of medical information using PHR. By recording the symptoms and physical conditions that occur during adjuvant hormonal therapy on the PHR, patients can share the recorded information with their physicians. Then, physicians can easily collect these lines of information on patients occurring at home, based on the records on PHR. Therefore, we used PHR as a tool for patients to easily interact with their physicians when receiving adjuvant hormonal therapy.

The use of both PHR and PRO was expected to help medical staff recognize any side effects early, and thus facilitate prompt and effective management of negative adverse events, resulting in the improvement not only of the quality of hormonal therapy but also the QoL of the patient. However, it has not yet been confirmed whether PHR is easily useable and convenient for breast cancer patients as a device to record their status, including adverse events and medication, during adjuvant hormonal therapy.

Therefore, the present study investigated whether patients who received adjuvant hormonal therapy could record their physical condition and daily medications as PRO on the PHR application (PHR app) during treatment. The patients were asked to input symptoms at home and daily records of medication into the PHR app. The effect of using the PHR app on the QoL of patients was assessed. Furthermore, patients were asked to answer a questionnaire to collect opinions on the use of the PHR app after the study period.

Materials and Methods

Study Design

This was a prospective study conducted at Showa University Hospital in patients with breast cancer who were treated with adjuvant hormonal therapy. The study period was set to one month from the initiation of adjuvant hormonal therapy. Before the beginning of the study period, patients installed the PHR app on their smartphones or tablets. We employed the cancer notebook application "Welby MyKarte ONC"" (Welby, Tokyo, Japan), which can be freely used by anyone, as a PHR app (Figure 1). Researchers examined the daily medications and symptoms of patients recorded on the PHR app during the study period. Patients were also asked to complete a questionnaire to collect impressions and opinions regarding the PHR app after use.

The study protocol was approved by the Ethics Committee of Showa University (approval no: 3235). All patients provided written informed consent to use their medical information and PHR app data for research purposes. The study was registered at the University Hospital Medical Information Network-Clinical Trials Registry Japan (UMIN000042365).

Patients

All patients, who were diagnosed with breast cancer and underwent any type of surgery at Showa University Hospital before starting adjuvant hormonal therapy and were aged 20 years or older were asked to participate. Patients who received radiotherapy between surgery and initiation of hormonal therapy were also eligible for the study. These patients were administered tamoxifen, anastrozole, letrozole, or exemestane as adjuvant hormonal therapy.

Treatment

The adjuvant hormonal therapy administered to patients was as follows: (1) tamoxifen at a dose of 20–40 mg once daily (1); (2) anastrozole at a dose of 1 mg once daily; (3) letrozole at a dose of 2.5 mg once daily; or (4) exemestane at a dose of 25 mg once daily (13).

QOL Measures

The Functional Assessment of Cancer Therapy-Breast (FACT-B) was used to evaluate the QoL of patients, because the FACT-B has been confirmed for its reliability and validity in a QoL study, and the FACT-B questionnaire was translated into Japanese (14-16). QoL was evaluated twice during the one-month of study period, firstly, just before the initiation of the hormonal therapy, 'before the use of PHR app (defined as Pre)', and secondly, one-month after the initiation of the therapy, 'after the use of PHR app (defined as Post)'.

The Records of Daily Medications

The records of daily medications were calculated by dividing the number of days that the patients recorded their medications on the PHR app by the number of treatment days (31 days).

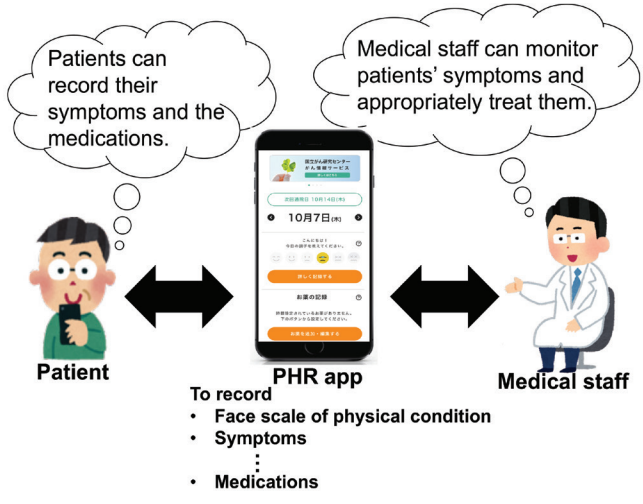

Figure 1. Interaction of patients with medical staffs using PHR app (Welby MyKarte ONC®).

PHR: the personal health record; app: application

The records of PROs

Patients recorded physical conditions and symptoms as PROs occurring at home during the one-month of study period on the PHR app.

Questionnaire

The questionnaire was collected via e-mail after completing the use of the PHR app. The questionnaire was designed to ask the following questions: 1) whether the patients usually feel a difficulty in communicating with medical staff, 2) whether the patients want to use the PHR app to communicate with medical staff to report their adverse events in the future, and 3) whether the patients want to use the PHR app in their daily lives.

Statistical Analysis

All **s**tatistical analyses were performed using JMP Pro software, version 15.0.0 (SAS Institute, Cary, NC, USA). The intra-patient changes in QoL scores between the beginning and the end of the study were analyzed using paired non-parametric Wilcoxon signed-rank test.

Results

Patient Characteristics

Fourteen patients were assessed between October 2020 and December 2020 for their eligibility to participate in this study. Table 1 shows the characteristics of the patients included in this study. All patients were positive for hormone receptors and received tamoxifen, anastrozole, or letrozole as adjuvant hormonal therapy. Nine patients were administered tamoxifen, four patients letrozole, and one patient anastrozole. Three and ten patients received neoadjuvant chemotherapy and radiotherapy, respectively, before starting adjuvant hormonal therapy.

QOL Scores Recorded Before and After the Use of PHR App

All 14 patients could use the PHR app installed on their smartphones or tablets for the study period. QoL scores of patients evaluated with FACT-B were recorded before (pre) and after (post) the use of the PHR app and are shown in Figures 2a to 2j. Physical well-being (PWB) scores were significantly higher at Post than at Pre ($p = 0.035$). In one patient, the PWB score at Post was 10 points higher than that at Pre. PWB scores calculated without this patient were not significantly different between pre and post. We investigated the causes of the 10-point increase in PWB score from pre to post observed in this patient and it was found that this patient had the lowest pre-PWB score among all patients (Figure 2a). Therefore, we first focused on the background of this patient before initiating hormonal therapy to determine the causes of these phenomena. Scores observed at pre for questions 3, 4, 5, and 6 were two points lower than the corresponding post score. According to the medical record, this patient received radiotherapy from the surgery performed a month earlier until just before starting the adjuvant hormonal therapy. The patient suffered from itching, dryness, and redness of the skin on the last day of radiotherapy, probably due to radiation exposure, which is thought to be the reason behind the low PWB score at pre. Details of the changes in the respective scores are shown in Table 2. The scores for social well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and breast cancer subscale (BCS) were not significantly different between pre and post.

Overall, the results indicated that the use of the PHR app did not negatively affect the QoL of patients.

Analysis of Questionnaire Performed After the Use of PHR App

The questionnaire responses conducted after the use of the PHR app are shown in Table 3. According to the answers to question 1 (whether the patients usually feel difficulties communicating with medical staff), there were seven patients who usually felt difficulty communicating with medical staff. Six (86%) out of these seven patients answered that they wanted to use the PHR app to communicate with medical staff (question 2, whether the patients wanted to use the PHR app

Table 1. The demographic and clinical characteristics of the fourteen patients participating in the study

		n (%)
Median age (range), years		50.7 (31–65)[a]
Marital status	Yes/no	9/5 (64.3/35.7)
Number of pregnancies	0 / ≥1	6/8 (42.9/57.2)
Working	Yes/no	12/2 (85.7/14.3)
Menopausal status	Pre/post	10/4 (71.4/28.6)
Comorbidity	(+)/(-)	6/8 (42.9/57.1)
Mastectomy	Partial/total	7/7 (50.0/50.0)
Stage group	I/II	9/5 (64.3/35.7)
Lymph node metastasis	Yes/no	5/9 (35.7/64.3)
Neoadjuvant chemotherapy	Yes/no	3/11 (21.4/78.6)
Radiotherapy	Yes/no	10/4 (71.4/28.6)
Drug for adjuvant hormonal therapy and daily doses	Tamoxifen 20 mg	9 (64.3)
	Anastrozole 1 mg	1 (7.15)
	Letrozole 2.5 mg	3 (21.4)
	Letrozole 2.5 mg + leuprorelin 11.25 mg	1 (7.15)

[a] : median (range); n: number

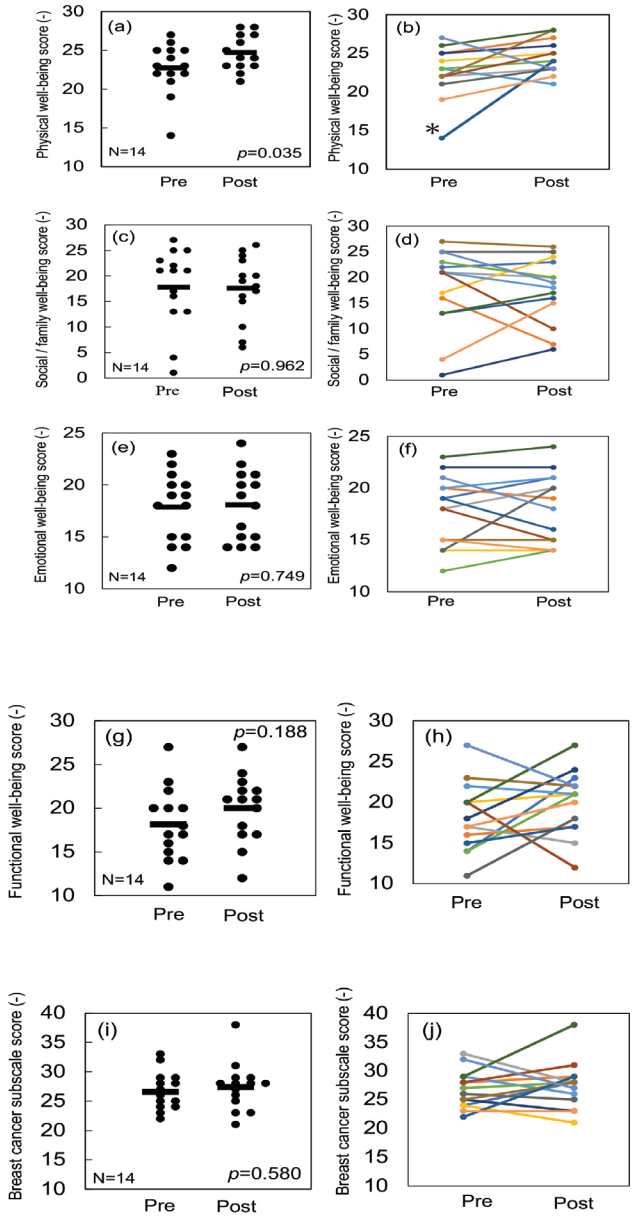

Figure 2. Effects of the PHR app use on QoL. Changes in QoL between pre and post were evaluated in 14 patients.

Panel **(a)** shows the plots of the PWB scores at pre and post. Panel **(b)** depicts the changes in the PWB observed in each patient from pre to post. One patient showed a 10-point increase in PWB from pre to post (*). Pairs of panels **(c, d), (e, f), (g, h)**, and **(i, j)** show similar results to **(a, b)** for social well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and breast cancer subscale (BCS), respectively. The statistical differences in the respective scores between pre and post shown in panels a, c, e, g, and i were analyzed using the Wilcoxon test.

pre: Just before the initiation of the hormonal therapy, that is, before the use of the PHR app; post: One month after the initiation of the therapy, that is, after the use of the PHR app. Bars indicate mean values; PHR: the personal health record; app: application; QoL: quality of life; PWB: physical well-being

to communicate with medical staff to inform their adverse events in the future). In addition, the reasons why patients answered "Yes" to question 2 are shown in Figure 3. Six patients wanted to use the PHR app as a communication tool for reasons, including: (1) to easily record their physical conditions; and (2) to avoid forgetting to share their physical conditions with medical staff. These results indicate that patients who have difficulty communicating with medical staff, want to use the PHR app to conveniently communicate with medical practitioners. On the other hand, three of six patients who did not feel difficulties in communicating with medical staff (question 1) answered "Yes" to question 2. According to Figure 3, these patients wanted to use the PHR app to communicate with medical staff in a timely and precise manner, even though they did not feel difficulties communicating with medical staff previously.

Next, we asked patients whether they wanted to continuously use the PHR app in the future (question 3) (Figure 4). In this question we did not restrict the use of the PHR app as a communication tool with medical staff as in question 2. Among the nine patients who answered "Yes" to question 2, eight (89%) wanted to continuously use PHR app in their future daily life. Four out of eight (50%) patients answered that they could record daily physical conditions on the PHR app and easily communicate with medical staff, similar to their answer to question 2. On the other hand, two of eight patients (25%) wanted to use the PHR app to avoid forgetting to take tablets during adjuvant hormonal therapy, suggesting there would be an improvement in medication adherence when using this application.

Daily Medications Recorded on PHR App

The daily records of medications reported on the PHR app are shown in Figure 5. Seventy-nine percent (11/14) recorded the intake of medicine for more than 28 days (≥ 90% of the days) during the study period (31 days). Two patients who wanted to use the PHR app to avoid forgetting to take a medicine (question 3) recorded 94 and 100% ($ sign in Figure 5). In contrast, two patients who recorded 0 and 40% did not want to use the PHR app in their daily lives (# sign in Figure 5). These results suggest that the use of the PHR app may support the maintenance of medication adherence for patients who would like to use the PHR app and to keep records of medication on it.

The PROs Recorded on PHR App

The physical conditions and symptoms recorded on the PHR app during the study period are shown in Table 4. The most typical adverse events of hormonal therapy are indicated by asterisks. Typical side effects induced by hormonal therapy, such as joint pain, hot flashes, and depression, occurred which worsen the QoL of the patients.

Discussion and Conclusion

In this prospective study, we examined whether patients with breast cancer could record their PROs, including their physical conditions and adverse events, on the PHR app during adjuvant hormonal therapy. We also examined the effects of the use of the PHR app on patients perceived QoL. The findings indicate that all patients could use the PHR app installed on their smartphones or tablets during the study period, without any negative effects on their QoL (Figure 2). The results suggest that PHR app-based interventions are feasible for patients who receive adjuvant hormonal therapy. Furthermore, the answers of patients to the questionnaire conducted after the use of the PHR app showed that approximately 70% wanted to use the PHR app in the future to communicate with medical staff to

report adverse events (Table 3). Ninety percent of these patients felt they experienced difficulty when communicating with medical staff (Figure 3). However, one patient who usually experienced difficulties in communicating with medical staff did not want to use the PHR app, because this patient usually recorded her physical conditions in a notebook. These results suggest that the PHR app might be a useful communication tool, especially for patients who cannot easily communicate with medical staff and do not have other means of recording that they have taken their medications. Additionally, two patients wanted to use the PHR app to remind themselves and to avoid forgetting to take medicines (Figure 4). Patients can record the intake of medical drugs on the PHR app and later they can confirm the entered data by themselves weekly. The PHR app also has an alarm function that allows patients to set the time they are supposed to take

Table 2. Change in each PWB score from Pre to Post in a patient with an increase in total PWB score of 10 points

Physical well-being questionnaire	PWB scores	
	Pre	Post
1. I have a lack of energy.	2	3
2. I have nausea.	4	4
3. Because of my physical condition, I have trouble meeting the needs of my family.	2	4
4. I have pain.	1	3
5. I am bothered by side effects of treatment.	1	3
6. I feel ill.	1	3
7. I am forced to spend time in bed.	3	4
Total	14	24

Pre: just before the initiation of the hormonal therapy, that is, before the use of PHR app; Post: one-month after the initiation of the therapy, that is, after the use of PHR app; PWB: physical well-being

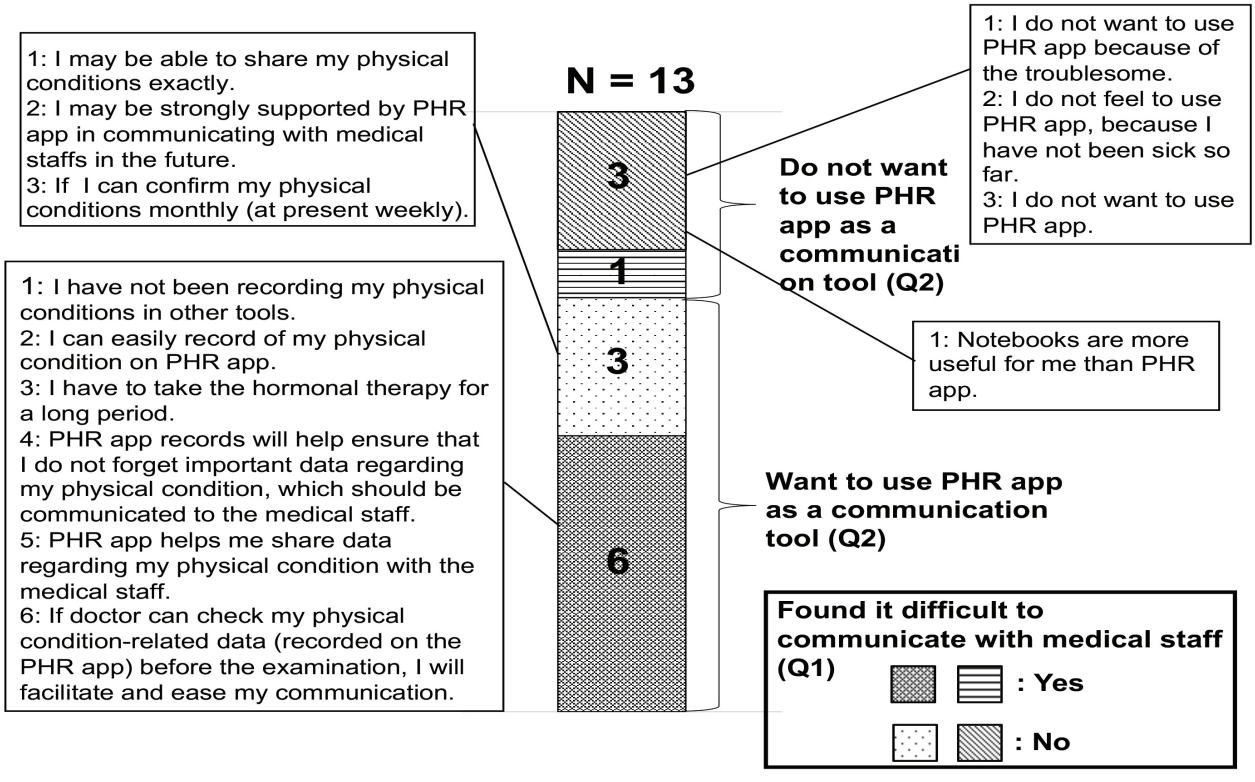

Figure 3. The answers of patients to question 2

Question 2: Whether the patients want to use the PHR app to communicate with medical staffs to inform their adverse events in the future.

PHR: the personal health record; app: application; N: number

their medicines. These PHR app functions will help prevent patients from forgetting to take their medications. Therefore, we believe that the PHR app may support medication adherence. Finally, the PROs recorded by the subjects on the PHR app were similar to the typical side effects induced by hormonal therapy, which lead to reduced QoL for patients (5). Taking these results into account, the PHR app might be a useful tool in terms of helping patients to communicate with medical staff and maintain their medication adherence.

One of the features of PHR use is that medical staff can monitor patient conditions remotely, unlike when patients use a written personal notebook. In other words, if patients continuously report severe adverse events on PHR, medical staff can reply promptly to any inquires they have and offer proper advice.

We believe that the following strategies might increase the usefulness of the PHR app in managing hormonal therapy. Firstly, to maintain patients' QoL effectively, it is necessary to establish a system where the medical staff routinely monitor PROs recorded on the PHR app and appropriately and promptly examine patients to avoid deterioration of the symptoms. There has been an attempt to monitor chemotherapy-induced side effects in patients with breast or colorectal cancer that occurred at home by using an online system on their personal computer or mobile device (17). In the study, nurses called patients to hear their

Table 3. Answers of 13 patients to the questions 1 to 3

Question	Answer	n (%)
1. Whether the patients usually feel difficulties to communicate with medical staff.	Yes	7 (53.8)
	No	6 (46.2)
2. Whether the patients want to use the PHR app to communicate with medical staff to report their adverse events in the future.	Yes	9 (69.2)
	No	4 (30.8)
3. Whether the patients want to use the PHR app in their daily lives.	Yes	8 (61.5)
	No	5 (38.5)

n: number; PHR: the personal health record; app: application

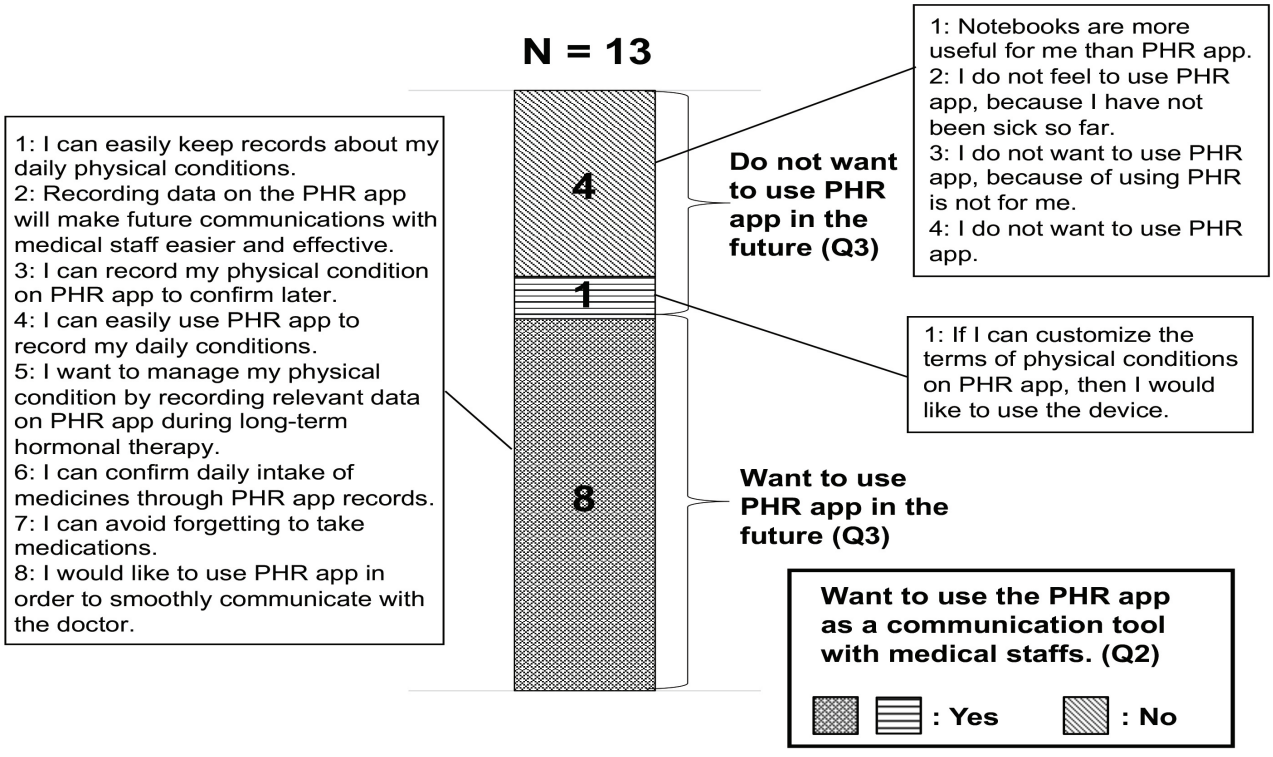

Figure 4. The answers of patients to question 3

Question 3: Whether the patients want to use the PHR app in their daily lives.

PHR: the personal health record; app: application; N: number

Table 4. The symptoms reported by 14 patients during the study period which ran for 31 days

Treatment periods of hormonal therapy (days)							
1 to 7		**8 to 14**		**15 to 21**		**22 to 31**	
Sleepiness	5 (35.7)[a]	Sleepiness	4 (28.6)	Hot flashes*	2 (14.3)	Headache	2 (14.3)
Dullness	3 (21.4)	Dullness	4 (28.6)	Headache	2 (14.3)		
Pain	3 (21.4)	Headache	3 (21.4)	Dullness	2 (14.3)		
Headache	2 (14.3)	Hot flashes*	2 (14.3)	Sleepiness	2 (14.3)		
Nausea	2 (14.3)	Nausea	2 (14.3)	Anxiety*	1 (7.15)		
Difficulty breathing	2 (14.3)	Joint pain*	1 (7.15)				
Itchy skin	2 (14.3)	Mood swings*	1 (7.15)				
Mood swings*	2 (14.3)	Anxiety*	1 (7.15)				
Anxiety*	2 (14.3)						
Joint pain*	1 (7.15)						

[a]Number of patients who recorded symptoms during the study periods (%); *Typical side effects induced by hormonal therapy which are known to be associated with the decrease in QoL; QoL: Quality of life

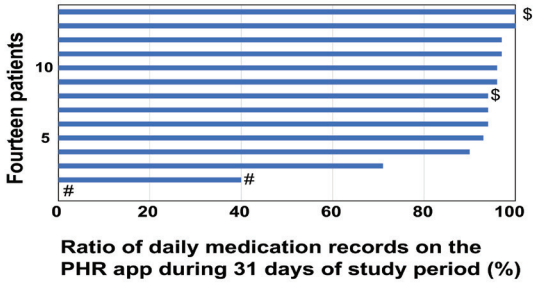

Figure 5. Ratio of daily medication records on the PHR app during study period. The daily medication records were measured in 14 patients. The ratio was calculated from number of days on which the patients recorded their medications on the PHR app divided by 31 days, which was the total study period.

$: Two patients who answered question 3 as "Yes", that is these patients wanted to use PHR app to prevent forgetting to take medicines; #: Two patients who answered question 3 as "No", that is these patients did not want to use PHR app

PHR: the personal health record; app: application

conditions when the medical staff recognized the patient reports indicating grade 3 or higher side effects, graded by PRO-common terminology criteria for adverse events. Appropriate and timely advice from nurses to patients could improve their QoL. Patients who receive hormonal therapy generally visit the hospital less frequently than those who are treated with chemotherapy. Consequently, medical staff have limited opportunities to understand the conditions of patients. Therefore, the use of the PHR app in hormonal therapy may have the potential to appropriately manage patients staying at home to maintain their QoL. It may be helpful for medical staff to monitor PROs if the system is incorporated into the electronic medical record system. A second strategy to appropriately maintain medication adherence of patients could involve medical professionals confirming the daily medication records that are reported on the PHR app by patients and provide advice based on the records. In a meta-analysis, mutual sharing of information related to medical adherence between patients and medical staff effectively improved medication adherence in adjuvant hormonal therapy (18). Considering this previous result, we believe that a system where patients and their doctors can share the daily medication records on the PHR app would be beneficial.

The present study had several limitations. First, the sample size was small, because this was an exploratory study, although it was performed in a prospective manner. Second, the study period was relatively short (one month). To evaluate the usefulness of the PHR app during the entire period of hormonal therapy, it is necessary to examine whether the patients can continuously use the PHR app for a long period. Third, this single-arm prospective study did not include control patients who did not use the PHR app. To overcome these limitations, we have already started a randomized control trial with a large number of patients.

In conclusion, all patients were able to use the PHR app without any negative effects on the reported QoL. PROs were recorded appropriately on the PHR app by most patients. The questionnaire revealed that most patients, especially those who had difficulty communicating with medical staff previously, wanted to use the PHR app to share their adverse events with medical staff. Some patients wanted to utilize the PHR app in order to avoid forgetting to take medications. Taken together, we conclude that the PHR app can be applied as a communication tool between patients and medical professionals in adjuvant hormonal therapy.

Acknowledgements

The auhors would like to thank all staff in the Division of Breast Surgical Oncology at Showa University Hospital for their assistance in various ways during the clinical study.

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Showa University (approval no: 3235). The study was registered at the University Hospital Medical Information Network-Clinical Trials Registry Japan (UMIN000042365).

Informed Consent: All patients provided written informed consent to use their medical information and PHR app data for research purposes.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.T., H.O., S.N., K.F.; Design: F.T., H.O., S.N., K.F.; Data Collection and/or Processing: F.T., H.O.; Analysis and/or Interpretation: F.T., H.O., S.N., K.F.; Literature Search: F.T., H.O.; Writing: F.T., H.O., S.N., K.F.

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

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

References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, Gray R, Clarke M, Cutter D, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011; 378: 771-784. (PMID: 21802721) [Crossref]
2. Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol 2010; 11: 1135-1141. (PMID: 21087898) [Crossref]
3. BIG 1-98 Collaborative Group; Mouridsen H, Giobbie-Hurder A, Goldhirsch A, Thürlimann B, Paridaens R, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J Med 2009; 361: 766-776. (PMID: 19692688) [Crossref]
4. Rosenberg SM, Stanton AL, Petrie KJ, Partridge AH. Symptoms and Symptom Attribution Among Women on Endocrine Therapy for Breast Cancer. Oncologist 2015; 20: 598-604. (PMID: 25933930) [Crossref]
5. Ochayon L, Zelker R, Kaduri L, Kadmon I. Relationship between severity of symptoms and quality of life in patients with breast cancer receiving adjuvant hormonal therapy. Oncol Nurs Forum 2010; 37: 349-358. (PMID: 20797943) [Crossref]
6. Henry NL, Azzouz F, Desta Z, Li L, Nguyen AT, Lemler S, et al. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. J Clin Oncol 2012; 30: 936-942. (PMID: 22331951) [Crossref]
7. Aiello Bowles EJ, Boudreau DM, Chubak J, Yu O, Fujii M, Chestnut J, et al. Patient-reported discontinuation of endocrine therapy and related adverse effects among women with early-stage breast cancer. J Oncol Pract 2012; 8: 149-157. (PMID: 23598850) [Crossref]
8. Hershman DL, Shao T, Kushi LH, Buono D, Tsai WY, Fehrenbacher L, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat 2011; 126: 529-537. (PMID: 20803066) [Crossref]
9. van Londen GJ, Donovan HS, Beckjord EB, Cardy AL, Bovbjerg DH, Davidson NE, et al. Perspectives of postmenopausal breast cancer survivors on adjuvant endocrine therapy-related symptoms. Oncol Nurs Forum 2014; 41: 660-668. (PMID: 25355021) [Crossref]
10. Kotronoulas G, Kearney N, Maguire R, Harrow A, Di Domenico D, Croy S, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol 2014; 32: 1480-1501. (PMID: 24711559) [Crossref]
11. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol 2016; 34: 557-565. (PMID: 26644527) [Crossref]
12. Detmer D, Bloomrosen M, Raymond B, Tang P. Integrated personal health records: transformative tools for consumer-centric care. BMC Med Inform Decis Mak 2008; 8: 45. (PMID: 18837999) [Crossref]
13. van de Velde CJ, Rea D, Seynaeve C, Putter H, Hasenburg A, Vannetzel JM, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet 2011; 377: 321-331. (PMID: 21247627) [Crossref]
14. Okamoto T, Shimozuma K, Katsumata N, Koike M, Hisashige A, Tanaka K, et al. Measuring quality of life in patients with breast cancer: a systematic review of reliable and valid instruments available in Japan. Breast Cancer 2003; 10: 204-213. (PMID: 12955032) [Crossref]
15. Brady MJ, Cella DF, Mo F, Bonomi AE, Tulsky DS, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. J Clin Oncol 1997; 15: 974-986. (PMID: 9060536) [Crossref]
16. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993; 11: 570-579. (PMID: 8445433) [Crossref]
17. Absolom K, Warrington L, Hudson E, Hewison J, Morris C, Holch P, et al. Phase III Randomized Controlled Trial of eRAPID: eHealth Intervention During Chemotherapy. J Clin Oncol 2021; 39: 734-747. (PMID: 33417506) [Crossref]
18. Finitsis DJ, Vose BA, Mahalak JG, Salner AL. Interventions to promote adherence to endocrine therapy among breast cancer survivors: A meta-analysis. Psychooncology 2019; 28: 255-263. (PMID: 30511789) [Crossref]

Original Article

Eur J Breast Health 2022; 18(2): 163-166
DOI: 10.4274/ejbh.galenos.2022.2021-11-6

The Benefit of Routine Axillary Sonographic Assessment in cN0 Breast Cancer Patients

Marian Khatib[1,2], Panagiotis Sgardelis[1], Schlomo Schneebaum[2], Ortal Schaffer[2], Richard Sutton[1]

[1]Breast Surgery Unit, Royal United Hospital, Combe Park, Bath, U.K.
[2]Department of Surgery, Tel-Aviv Sourasky Medical Center, Tel Aviv University, Sackler School of Medicine, Tel-Aviv, Israel

ABSTRACT

Objective: Axillary ultrasound (US) is often part of the routine assessment of the clinically negative axilla in primary breast cancer, which determines the extent of axillary surgery to be performed. This study aims to ascertain the burden of disease in the axilla of patients with a normal clinical examination (cN0) but with US detected metastatic axillary lymph nodes.

Materials and Methods: We retrospectively identified 345 female patients who underwent axillary lymph node dissection, following a positive lymph node biopsy, between January 2015 and August 2019.

Eighty-nine of those had a positive biopsy prior to surgery. They were divided into two groups: Those with clinically palpable axillary disease preoperatively, cN1 (n = 41), and those with a normal clinical axillary examination, cN0 (n = 48). We assessed the number of positive axillary lymph nodes dissected in the two groups.

Results: In the cN0 group the mean value of excised disease-positive axillary lymph nodes was 3.6, while in the cN1 group it was 8.0 (p<0.01). However, further analysis showed that 25 patients of the cN0 who had T1/T2 tumors had ≥3 positive lymph nodes.

Conclusion: Our study suggests that the presence of clinically palpable axillary lymph nodes appears to be correlated to a higher number of positive lymph nodes. However, in cases of non-palpable sonographically positive lymph nodes there might still be significant axillary disease, even in T1 and T2 tumors. Therefore we still support the routine use of preoperative sonographic assessment of the axilla for early breast cancer.

Keywords: Axilla; axillary dissection; breast ultrasonography; positive lymph nodes; sentinel node biopsy

Cite this article as: Khatib M, Sgardelis P, Schneebaum S, Schaffer O, Sutton R. The Benefit of Routine Axillary Sonographic Assessment in cN0 Breast Cancer Patients. Eur J Breast Health 2022; 18(2): 163-166

Key Points

- Palpable axillary lymph nodes might imply bigger axillary tumor burden.
- In cases of non palpable lymph nodes, there still might be significant axillary disease.
- Routine Sonographic assessment of the axilla in early breast cancer is essential, and might change the management.

Introduction

Axillary lymph node dissection (ALND) has high sensitivity as a technique for the detection of axillary metastatic disease in patients with breast cancer (1). However, it carries an increased risk of complications, such as lymphedema, nerve injury, wound infection, paresthesia and axillary seromas (2, 3).

In 1994 Giuliano et al. (1) showed that sentinel lymph nodes (SLN) were significantly more likely to contain metastasis than non-sentinel lymph nodes removed during ALND.

The sensitivity of sentinel lymph node biopsy (SLNB) for node involvement has been estimated to range between 71% and 100% with a false-negative rate of about 8.4% (4-6). One of the greatest advantages of SLNB is the near total absence of local postoperative complications, and long-term survival is at least equivalent to that after ALND (7-9).

Corresponding Author:
Marian Khatib; mariankh@gmail.com

Received: 19.11.2021
Accepted: 19.02.2022
Available Online Date: 01.04.2022

ALND was the standard of care for patients with SLN metastases until the Z0011 study was published (10). Patients with 1–2 SLN metastases who were planned for lumpectomy and whole breast post-operative radiotherapy were randomized to ALND or no further surgical treatment. Their results showed that axillary relapse after a median follow-up of 6.3 years was 1% in those who received no further axillary surgery.

Although the trial closed early and in spite of criticism of Z0011, it changed the practice of treating the axilla in many institutions worldwide, especially in North America (11).

The AMAROS trial is another study that was published in 2014 and showed that ALND and axillary radiotherapy after a positive SLN provide comparable axillary control for patients with T1-2 primary breast cancer and no palpable lymphadenopathy (12).

The current trend in the treatment of breast cancer is going towards minimizing axillary surgery, and ALND should no longer be considered routine management of the node-positive breast cancer patient (13, 14).

Staging of the axilla begins with a history and physical examination. Patients with impalpable axillary lymph nodes are defined as clinically lymph node negative (cN0).

There are differences in non-operative axillary staging in different parts of the world. European Society for Medical Oncology (ESMO) guidelines considers routine pre-operative axillary ultrasound +/- needle biopsy an integral part of the non-operative axillary staging for patients with non-palpable lymph nodes (14).

In our institution, ESMO guidelines are followed and routine axillary ultrasound (US) is performed as part of the assessment for primary breast cancer. Any suspicious lymph nodes identified on US are biopsied. The decision to proceed with an ALND is based on biopsy results; if the biopsy is positive for cancerous cells then the patient would undergo ALND as part of the primary procedure, whereas if the biopsy is negative then the patient would undergo SLNB first. This approach may mean, as suggested by some studies (15-17) that we are overtreating the axilla in cases where a positive US guided biopsy is due to micrometastasis or in the presence of 1–2 positive lymph nodes only (when the tumor size is T1 or T2), which according to Z0011 and AMAROS, ALND could be avoided without affecting nodal recurrence, disease-free survival, or overall survival (10-12, 18).

Purpose

The purpose of this study was to assess the clinical value and implications of sonographic assessment of the axilla in patients with a normal clinical axillary examination. We aimed to assess whether pre-operative US for cN0 patients, followed by a biopsy of abnormal appearing lymph nodes, leads to over treatment of the axilla.

Materials and Methods

We retrospectively identified 345 female patients who underwent ALND between January 2015 and August 2019 in our institution. The patients were identified using our institution's surgical operations database. Each patient's electronic medical records were reviewed and the following data were recorded: patient demographics; pre-operative clinical axillary examination findings; ultrasound findings; tumor size; histology and grade; and ALND pathology results.

Patients who received neo-adjuvant treatment (n = 213), patients who underwent ALND for a positive sentinel lymph node biopsy (n = 40) and patients who underwent ALND for axillary disease recurrence (n = 3) were excluded (Figure 1). Post neoadjuvant patients were excluded, because these patients underwent ALND post neoadjuvant, based on a positive lymph node biopsy prior to treatment, when some of them had complete or partial pathological response and including them would have biased our results.

Eighty-nine patients met the inclusion criteria and had a positive lymph node biopsy prior to surgery. They were analyzed in two distinct groups: those with clinically palpable axillary disease pre-operatively (n = 41), denoted as cN1, and those with a normal clinical axillary examination pre-operatively (n = 48), denoted as cN0 (Figure 1).

The Mann-Whitney non-parametric U test was used to compare ALND pathology results between the two groups.

Results

The patient records of the 89 patients who underwent ALND and met our inclusion criteria were reviewed. Forty-eight patients had ALND in the normal clinical axillary examination group (cN0). The mean number of excised, disease-positive axillary lymph nodes was 3.6 (range: 1–22). Further subgroup analysis showed that 23 of the cN0 patients had ≤2 positive lymph nodes and 25 patients had ≥3 positive lymph nodes. Forty-one cN0 patients had T1/T2 tumor size.

In the clinically palpable lymph node group, 41 patients had ALND. The mean number of excised, disease-positive axillary lymph nodes was 8.0 (range: 0–59). A summary of the data can be seen in Table 1.

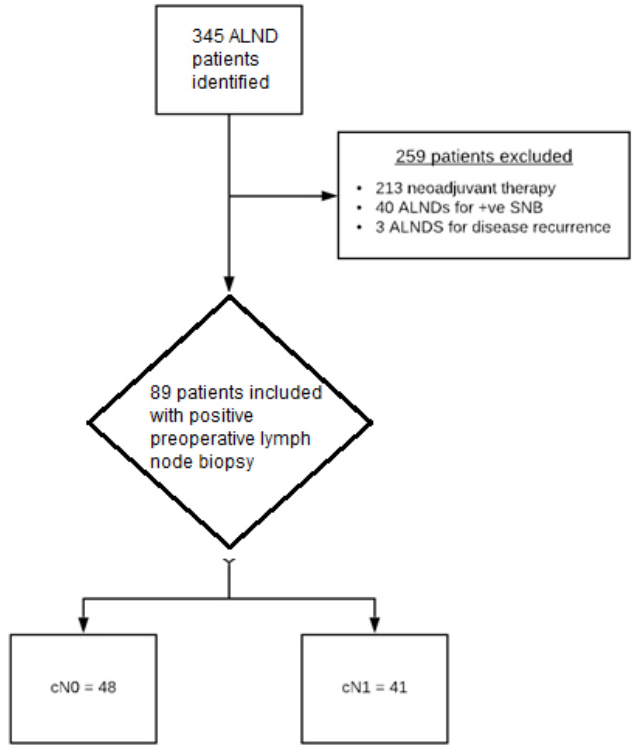

Figure 1. Flow diagram of patients included and excluded from the study

ALND: axillary lymph node dissection; SNB: sentinel lymph node biopsy

Table 1. Demographic and clinico-pathologic characteristics of included patient groups

Characteristics	cN0 group (n = 48)	cN1 group (n = 41)
Mean age in years (range)	59.8 (35–87)	64.2 (41–84)
Tumor histology		
Invasive ductal (IDC)	38	34
Invasive lobular (ILC)	7	5
Other	IDC & DCIS (2) IDC & ILC (1)	IDC & DCIS (2)
Tumor grade		
I	2	0
II	23	18
III	23	23
Mean ALND positive nodes (range)	3.6 (1–22)	8 (0–59)
Median ALND positive nodes	2	4
Tumor		
<2 cm	10	13
2–5 cm	31	19
>5 cm	7	9

ALND: Axillary lymph node dissection; DCIS: ductal carcinoma *in situ;* n: number

The Mann–Whitney test used for our statistical analysis resulted in a *p*-value of 0.008.

Discussion and Conclusion

Axillary lymph nodes status is important in the initial staging of breast cancer as a prognostic factor for overall survival and subsequent management (19, 20). However, there is no consensus regarding the extent of dissection necessary for adequate staging (21). We are living in an era of a paradigm shift from ALND being used as a therapeutic procedure to it being considered a staging procedure only. Updated Ontario Health (Cancer Care Ontario) and American Society of Clinical Oncology (ASCO) guideline algorithm for the management of the axilla in patients with early-stage (clinical stage T1, T2, N0 and N1 breast cancer) recommends SLNB for all patients, including patients with no palpable axillary nodes on physical examination who might have had an US that was equivocal, abnormal, or even biopsy-proven positive (22). However, updated ESMO Guidelines still recommend routine axillary sonographic assessment for all breast cancer patients (23); thus there is still no consensus on this matter.

Our data analysis suggests that the presence of clinically palpable lymph nodes appears to be correlated to a higher number of disease positive lymph nodes retrieved from axillary dissection (mean ALND positive of 8 in cN1 vs. 3.6 in cN0).

However, the number of positive lymph nodes in the cN0 group ranged between 1 and 22. While only 23 patients (48.9%) had two or less positive lymph nodes, the rest 51% (25 patients) had three or more.

This suggests that a significant axillary disease load may be present, even if the axilla is clinically normal on examination. Omitting axillary US might lead to missed axillary disease left untreated, and its effect on recurrence and survival is unknown.

In conclusion, the presence of clinically palpable lymph nodes in our group of patients was correlated to the axillary tumor load. Nearly half of the patients in our cN0 cohort had two or less metastatic lymph nodes. This might imply that in a certain group of patients with cN0 and a positive, pre-operative, US guided biopsy ALND could be spared, which matches the sixteenth St. Gallen International Consensus Guidelines (24). However, until a large prospective study is done to better define this subgroup of patients, we still support the routine use of pre-operative sonographic assessment of the axilla. Given the relative simplicity of US, lack of radiation, low cost and a relatively accurate means of staging, this seems reasonable, given the lack of definitive evidence either way.

Ethics Committee Approval: The project titled "Breast Cancer Assessment Protocol: Is routine sonographic evaluation of clinically normal axillae necessary?" was registered with our institutional review board at the Royal United Hospital, Bath, U.K. in July 2020 and was given the following ID number: 3434. As per our institutional policy, no ethics approval was required for this type of retrospective review.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: R.S.; Design: M.K.; Supervision: M.K., S.S., R.S.; Data Collection and/or Processing: M.K., P.S.; Analysis and/or Interpretation: M.K., P.S., S.S., R.S.; Literature Search: M.K.; Writing: M.K., P.S., O.S.; Critical Review: M.K., S.S., R.S.

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

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

References

1. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 1994; 220: 391-401. (PMID: 8092905) [Crossref]
2. Abass MO, Gismalla MDA, Alsheikh AA, Elhassan MMA. Axillary Lymph Node Dissection for Breast Cancer: Efficacy and Complication in Developing Countries. J Glob Oncol 2018; 4: 1-8. (PMID: 30281378) [Crossref]
3. Soares EW, Nagai HM, Bredt LC, da Cunha AD Jr, Andrade RJ, Soares GV. Morbidity After Conventional Dissection of Axillary Lymph Nodes in Breast Cancer Patients. World J Surg Oncol 2014; 12: 67. (PMID: 24670000) [Crossref]
4. I van der Ploeg IM, Nieweg OE, van Rijk MC, Valdés Olmos RA, Kroon BB. Axillary recurrence after a tumor-negative sentinel node biopsy in breast cancer patients: a systematic review and meta-analysis of the literature. Eur J Surg Oncol 2008; 34: 1277-1284. (PMID: 18406100) [Crossref]
5. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010; 11: 927-933. (PMID: 20863759) [Crossref]
6. Lyman GH, Giuliano AE, Somerfield MR, Benson AB 3rd, Bodurka DC, Burstein HJ, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005; 23: 7703-7720. (PMID: 16157938) [Crossref]
7. Schulze T, Mucke J, Markwardt J, Schlag PM, Bembenek A. Long-term morbidity of patients with early breast cancer after sentinel lymph node biopsy compared to axillary lymph node dissection. J Surg Oncol 2006; 93: 109-119. (PMID: 16425290) [Crossref]
8. Del Bianco P, Zavagno G, Burelli P, Scalco G, Barutta L, Carraro P, et al. Morbidity comparison of sentinel lymph node biopsy versus conventional axillary lymph node dissection for breast cancer patients: results of the sentinella-GIVOM Italian randomised clinical trial. Eur J Surg Oncol 2008; 34: 508-513. (PMID: 17614245) [Crossref]
9. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 2003; 349:546-553. (PMID: 12904519) [Crossref]
10. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011; 305: 569-575. (PMID: 21304082) [Crossref]
11. Lyman GH, Somerfield MR, Giuliano AE. Giuliano. Sentinel Lymph Node Biopsy for Patients with Early-Stage Breast Cancer: 2016 American Society of Clinical Oncology Clinical Practice Guideline Update Summary. J Oncol Pract 2017; 13: 196-198. (PMID: 28118104) [Crossref]
12. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014; 15: 1303-1310. (PMID: 25439688) [Crossref]
13. Morrow M. Management of the Node-Positive Axilla in Breast Cancer in 2017: Selecting the Right Option. JAMA Oncol 2018; 4: 250-251. (PMID: 29242929) [Crossref]
14. Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26(Suppl 5): 8-30. (PMID: 26314782) [Crossref]
15. Lyman GH, Temin S, Edge SB, Newman LA, Turner RR, Weaver DL, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2014; 32: 1365-1383. (PMID: 24663048) [Crossref]
16. Pilewskie M, Jochelson M, Gooch JC, Patil S, Stempel M, Morrow M. Is Preoperative Axillary Imaging Beneficial in Identifying Clinically Node-Negative Patients Requiring Axillary Lymph Node Dissection? J Am Coll Surg 2016; 222: 138-145. (PMID: 26711795) [Crossref]
17. Pilewskie M, Mautner SK, Stempel M, Eaton A, Morrow M. Does a Positive Axillary Lymph Node Needle Biopsy Result Predict the Need for an Axillary Lymph Node Dissection in Clinically Node-Negative Breast Cancer Patients in the ACOSOG Z0011 Era? Ann Surg Oncol 2016; 23: 1123-1128. (PMID: 26553439) [Crossref]
18. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women with Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA 2017; 318: 918-926. (PMID: 28898379) [Crossref]
19. Winer EP, Morrow M, Osborne CK, Harris JR. Malignant tumors of breast. In: Devita VT, Hellman S, Rosenberg SA, editors. Cancer Principles and Practice of Oncology, 6th ed. Philadelphia: Lippincot Williams and Wilkins; 2001.p.1651-726. [Crossref]
20. Kolscienly S, Le MG, Tubiana M. The natural history of human breast cancer. The relationship between involvement of axillary lymph nodes and initiation of distant metastases. Br J Cancer 1989; 59: 775-782. (PMID: 2736212) [Crossref]
21. Greenall MJ. How should the axilla be treated in breast cancer? Why I favour axillary node sampling in the management of breast cancer? Eur J Surg Oncol 1995; 21: 2-5. (PMID: 7851546) [Crossref]
22. Brackstone M, Baldassarre FG, Perera FE, Cil T, Chavez Mac Gregor M, Dayes IS, et al. Management of the Axilla in Early-Stage Breast Cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline. J Clin Oncol 2021; 39: 3056-3082. (PMID: 34279999) [Crossref]
23. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019; 30: 1194-1220. (PMID: 31161190) [Crossref]
24. Chen MY, Gillanders WE. Staging of the axilla in breast cancer and the evolving role of axillary ultrasound. Breast Cancer (Dove Med Press) 2021; 13: 311-323. (PMID: 34040436) [Crossref]

Original Article

Eur J Breast Health 2022; 18(2): 167-171
DOI: 10.4274/ejbh.galenos.2022.2022-1-4

Prognostic Value of Receptor Change After Neoadjuvant Chemotherapy in Breast Cancer Patients

Özlem Özdemir[1], Baha Zengel[2], Demet Kocatepe Çavdar[3], Cengiz Yılmaz[1], Raika Durusoy[4]

[1]Department of Medical Oncology, İzmir Bozyaka Training and Research Hospital, University of Health Sciences Turkey, İzmir, Turkey
[2]Department of General Surgery, İzmir Bozyaka Training and Research Hospital, University of Health Sciences Turkey, İzmir, Turkey
[3]Department of Medical Pathology, İzmir Bozyaka Training and Research Hospital, University of Health Sciences Turkey, İzmir, Turkey
[4]Department of Public Health, Ege University, Faculty of Medicine School, İzmir, Turkey

ABSTRACT

Objective: The aim of this study was to investigate the relationship between hormone receptors (HR) and human epidermal growth factor receptor 2 (HER-2) discordance with prognosis, before and after neoadjuvant chemotherapy (NAC) in breast cancer patients.

Materials and Methods: Histopathological data of 142 breast cancer patients attending a single center between 2001 and 2018 and were operated after NAC were evaluated retrospectively.

Results: The median (range) age of patients was 58 (32–69) years**.** In patients who underwent Tru-cut biopsy before NAC, 77 patients were ER+, 30 were ER (-), 73 were PR (+), 33 were PR-, 14 were HER-2 (+), and 94 patients were HER-2 (-). In terms of ER change, five patients were found to have changed status and 85 had no receptor change. The mean overall survival of patients with receptor changes was 31 months against 60 months in patients with no receptor changes, which was not significant (p = 0.351). In sub-group analysis of patients undergoing receptor change, the ER (+) → (–) group had significantly shorter survival (p = 0.003). For PR change, mean survival was 38 months in seven patients with a receptor change and 59 months in 87 patients without a receptor change, which was not significant (p = 0.603). Sub-group analysis of PR status change showed that survival was significantly shorter in the PR (+) → (–) group (p = 0.012).

Conclusion: These results suggest there is a need for reassessment of HR and HER-2 status in surgical samples from patients following NAC, and that NAC-induced changes in the HR state may be used as a prognostic factor.

Keywords: Breast cancer; neoadjuvant chemotherapy; estrogen receptor; progesterone receptor; receptor change

Cite this article as: Özdemir Ö, Zengel B, Kocatepe Çavdar D, Yılmaz C, Durusoy R. Prognostic Value of Receptor Change After Neoadjuvant Chemotherapy in Breast Cancer Patients. Eur J Breast Health 2022; 18(2): 167-171

Key Points

- Neoadjuvant chemotherapy might change the status of breast cancer biomarkers, including estrogen receptor (ER), progesterone receptor (PR), and HER-2.
- Receptor status change, the ER (+) → (–) and PR (+) → (–) patients had significantly shorter overall survival.
- There was no statistical relationship between the change of Ki-67 level and survival.

Introduction

The advantages of neoadjuvant treatment, such as the treatment of distant micrometastases, regression in tumor stage, increased operability, and increased chances of breast-conserving surgery, has meant it has become a standard for locally advanced breast cancer (1-3). Although neoadjuvant chemotherapy (NAC) treatment in local or locally advanced breast cancer does not have a disease-free survival (DFS) or overall survival (OS) superiority over adjuvant treatment, the achievement of a pathological complete response (pCR) is associated with prolonged survival (4, 5). In many studies investigating NAC treatment response, estrogen receptor (ER) status has been considered a determinant marker of chemosensitivity, and it has been shown that ER negativity can predict treatment response (6, 7). In a retrospective study of 1,731 patients,

Corresponding Author:
Özlem Özdemir; ozdemirozlem.md@gmail.com

Received: 27.01.2022
Accepted: 23.02.2022
Available Online Date: 01.04.2022

the pCR rate for ER-negative patients was 24%. However, ER-positive patients responded at a rate of 8%. In terms of pCR, despite the different chemotherapy regimens administered, ER negativity has been highlighted as a predictive factor, independent of treatment (8). National Surgical Adjuvant Breast and Bowel Project (NSABP) B27 and NSABP B18 studies also showed higher pCR rates in hormone receptor (HR) negative patients compared to HR-positive patients (9, 10). The effectiveness of anthracycline-based and taxane-based treatments as neoadjuvant treatment is known in breast cancer. Since triple-negative breast cancer and human epidermal growth factor receptor 2 (HER-2) positive breast cancer are more chemosensitive, they benefit from the neoadjuvant treatment to a higher extent and pCR is reported to occur at higher rates. However, the fact remains that only a small proportion of patients following NAC treatment achieve pCR, while most patients treated with NAC still have residual disease (11). Recent studies have reported levels of discordance between HR and HER-2, before and after NAC treatment (12-14). It is debatable whether post-NAC changes in breast cancer biomarkers, such as HRs and HER-2 affect patient prognosis. The aim of this study was to evaluate the prognostic value of pre- and post-NAC ER, Progesterone Receptor (PR) and HER-2 receptor changes and assess these in respect of clinical outcome.

Materials and Methods

Histopathological data of breast cancer patients who attended our clinic between 2001 and 2018 and were operated after NAC were evaluated retrospectively. The majority of patients (more than 90%) were referred from 2010 onwards, and about a quarter of the Tru-cut biopsies were taken by external centers. The study included only the patients whose Tru-cut biopsies were performed and histopathology examined in our hospital. We identified 142 patients diagnosed with primary breast cancer who had any residual disease in the breast and/or lymph nodes after receiving NAC, and pathology reports containing the ER, PR, and HER-2 status of pretreatment core needle biopsy (CNB) and residual tumor. We reviewed these patient's medical records for clinicopathological data. All pathological specimens, including the immunohistochemistry (IHC) slides from outside the institution, were reviewed by dedicated breast cancer pathologists. Patients with pCR were excluded.

Data items collected included demographic data (gender, age, and contact information), surgical procedure, histopathological and immunohistochemical characteristics, systemic adjuvant/neoadjuvant therapy and follow-up duration. The American Joint Committee on Cancer (AJCC) TNM grading system was used for staging. Immunohistochemical analysis of ER, PR, HER-2, Ki-67 proliferation index was performed. At least 1% of tumor cells being stained were considered ER and PR positive, and immunohistochemical staining 3+ was considered HER-2 (+). However, in cases with immunohistochemical HER-2 +2, fluorescent *in situ* hybridization (FISH) was performed. For cases in the study, the threshold value for Ki-67 immunochemical staining was taken as 14% (15). Changes in HR and HER-2/neu status were evaluated in terms of response to survival. This study followed the Declaration of Helsinki in terms of medical protocol and ethics and the regional Ethical Review Board approved the study. Before the study, approval was obtained from the clinical research ethics committee of our hospital.

Statistical Analysis

In statistical analysis, SPSS for Windows, version 11.5 was used (IBM Inc., Armonk, NY, US). The categorical measurements were summarized as number and percentage, and the continuous measurements were summarized as mean and standard deviation. Categorical variables were compared using the chi-square test or Fisher's exact test. The Kruskal–Wallis test was used on the parameters that were not normally distributed, followed by paired comparisons of the groups with Mann–Whitney U test. Pre- and post-chemotherapy comparisons were made using the Wilcoxon test. Overall survival (OS) was analyzed with the Kaplan–Meier test, and survival curves were compared with the log-rank test. *P*-values <0.05 were accepted as significant.

Results

The average age of patients was 58 at the time of diagnosis (min: 32, max: 69). The average follow-up time was 29±17 (range: 5–97) months. Table 1 shows the number of patients tested, and the number of patients positive or negative for ER, PR, HER-2 and their Ki-67 status.

The post-NAC receptor and Ki-67 changes of the patients are shown in Table 2. The mean overall survival of patients with receptor changes was 31 months against 60 months in patients with no receptor changes. However, this difference was statistically insignificant ($p = 0.351$).

The receptor status of five patients changed in terms of ER, while 90 patients underwent no change in ER receptor status. In sub-group analysis of the ER receptor change, the ER(+) → (-) patients had a significantly shorter survival ($p = 0.003$). Similarly, PR status changed in seven patients while 87 maintained their pre-NAC receptor status. Mean overall survival (mOS) was 38 months in these seven patients

Table 1. Receptor distribution in pre-NAC Tru-cut biopsy sample

ER		PR		HER-2		Ki-67	
107		106		108		104	
(+)	(-)	(+)	(-)	(+)	(-)	≥15	<15
77	30	73	33	14	94	83	21
72%	28%	69%	31%	13%	87%	80%	20%

ER: estrogen receptor; PR, progesterone receptor; HER-2: human epithelial growth factor 2 receptor; NAC: neoadjuvant chemotherapy

Table 2. Receptor distribution in post-NAC operation material

ER		PR		HER-2		Ki-67	
112		112		111		100	
(+)	(-)	(+)	(-)	(+)	(-)	≥ 15	< 15
87	25	77	35	20	91	60	40
78%	22%	69%	31%	18%	82%	60%	40%

ER: estrogen receptor; PR, progesterone receptor; HER-2: human epithelial growth factor 2 receptor; NAC: neoadjuvant chemotherapy

with a receptor status change but 59 months in 87 patients without a receptor change, which was statistically insignificant (p = 0.603). Sub-group analysis of patients experiencing a PR status change showed that survival was significantly shorter in the PR (+) → (-) group (p = 0.012) (Table 3). The total rate of change in the post-NAC treatment of ER (+) patients was (5/95) ≅ 5%, and the total rate of PR change was (7/94) ≅ 7%. In terms of HER-2 change, mean survival was 66 months in 14 patients with HER-2 change and was 57 months in patients with no change (p = 0.442). Finally, 25% of the patients with pre-NAC Ki-67 ≥15% presented post-NAC Ki-67 as ≤14% and 33% of the patients with pre-NAC Ki-67 level ≤14% were found to be ≥15% after treatment but no relationship was detected between these changes and survival (Table 4).

Discussion and Conclusion

In this study, the pre- and post-NAC receptor status change rates were ~5% for ER, ~7% for PR, and ~17% for HER-2. In sub-group analysis of patients undergoing receptor status change, the ER (+) → (-) and PR (+) → (-) patients had significantly shorter overall survival. The results of various studies concerning the prognostic value of such post-NAC changes in these receptor levels are controversial. In the compilation published by van de Ven et al. (16), they reported

Table 3. Receptor change rate after NAC

	ER (+)[a]		ER (-)[b]		PR (+)[c]		PR (-)[d]		HER-2 (+)[e]		HER-2 (-)[f]		Ki-67 (≥15)[g]		Ki-67 (<15)[h]	
n	69		26		64		30		12		84		64		15	
	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	≥15	<15	≥15	<15
	68	1	4	22	60	4	3	27	8	4	12	72	48	16	5	10

[a] ER (+) patients; Post NAC ~ 1.4% NEGATIVE

→ TOTAL ER CHANGE RATE (5/95) ≅ 5.3%

[b] ER (-) patients; Post NAC ~ 15.4% POSITIVE

[c] PR (+) patients; Post NAC ~ 6% NEGATIVE

→ TOTAL PR CHANGE RATE (7/94) ≅ 7.4%

[d] PR (-) patients; Post NAC 10% POSITIVE

[e] HER-2 (+) patients; Post NAC 33% NEGATIVE

→ TOTAL HER-2 CHANGE RATE (16/96) ≅16.7%

[f] HER-2 (-) patients; Post NAC 14% POSITIVE

[g] Ki-67 ≥ 15 ; Post NAC 25% < 15

→ TOTAL Ki-67 CHANGE RATE WAS 26%

[h] Ki-67 <15 ; Post NAC 33% ≥ 15

ER: estrogen receptor; PR, progesterone receptor; HER-2: human epithelial growth factor 2 receptor; NAC: neoadjuvant chemotherapy

Table 4. The effect of receptor change before and after NAC on prognosis

	ER	PR	HER-2
Total number of patients	95	94	96
Patient with changed receptor, n (%)	5 (5.3)	7 (7.4)	16 (16.7)
Change to negative	1	4	4
Change to positive	4	3	12
mOS receptor status change (months)	31	38	57
mOS receptor status unchanged (months)	60	59	77
	p = 0.351	p = 0.603	p = 0.447

Survival was shorter in the subgroup that became ER negative after NAC when they had been ER positive prior to NAC (p = 0.003).
Survival was shorter in the subgroup that became PR negative after NAC when they had been PR positive prior to NAC (p = 0.012).
ER: estrogen receptor; PR: progesterone receptor; HER-2: human epithelial growth factor 2 receptor; NAC: neoadjuvant chemotherapy; mOS: mean overall survival; n: number

discordance rates of ER, PR and HER-2 status of 2.5%–17%, 5.9%–51.7% and 2.3%–35%, respectively. Another meta-analysis indicated ER and PR changes during NAC (17). Finally, a large-scale retrospective study showed that approximately 21.4% of HER-2 (+) patients have become HER-2 (-) in the metastatic region (18). The results of various studies related to the prognostic value of post-NAC changes in the status of these receptors are controversial. Most studies concluded that HR (+) → (-) patients have a worse prognosis in terms of both OS and DFS (19). However, Tacca et al. (20) observed no significant change in DFS or OS between HR (-) → (+) and HR (-) → (-) patients.

Prognosis is poor in cases with a high index of Ki-67 proliferation, which is one of the most important prognostic parameters in breast cancer. Available studies show that the Ki-67 score generally changes after NAC (21-23). A study conducted by Arens et al. (24) on a small sample (n = 25) reported an insignificant change in post-NAC Ki-67 expression, while Burcombe et al. (21) detected a significant relationship between post-NAC Ki67 decrease and the pathological response. In our study, the post-NAC Ki-67 change rate was 26% and there was no statistical relationship between the change of Ki-67 level and survival.

HER-2 overexpression or amplification is detected in 15%–25% of all breast cancers, and HER-2 positivity in breast cancer is associated with poor prognosis, resistance to standard treatments, early recurrence risk, shorter DFS and shorter OS (2, 3). In a recent study, Tiezzi et al. (25) reported a significant relationship between the overexpression of HER-2 protein and DFS and OS in breast cancer patients. On the other hand, they detected no change in HER-2/neu expression after NAC. Similarly, Zhao et al. (26) and Arens et al. (24) failed to report any changes in HER-2 status after NAC (24, 26, 27). A meta-analysis performed by Li et al. (27) showed that HR and HER-2 were lost or gained in a significant portion of the patients after receiving NAC. It was reported to be noteworthy that after NAC 13.8% and 2.6% of patients gained ER or HER-2 positivity, respectively (24). On the other hand, HR+ → – patients in the meta-analysis had both worse DFS and OS compared to HR (+) → (+) patients. These authors suggested that shorter DFS and OS and HR loss in HR (+) → (-) patients could suggest a more aggressive phenotype.

At present there is no consensus on whether adjuvant endocrine treatment is required for patients with HR changes following NAC treatment. Regarding the adjuvant endocrine therapy, there is a general approach for administering hormonal therapy whenever HR are positive. There was only one retrospective study (28) designed to investigate the value of adjuvant endocrine treatment in HR (+) → (-) patients (57 patients were treated for endocrine and 40 patients were not treated for endocrine). The DFS of the adjuvant endocrine treatment group was significantly higher than of the non-adjuvant endocrine treatment group. However, the 5-year OS rate was not different statistically. Therefore, further studies and future research are required to understand the role of adjuvant endocrine treatment for HR+ → – patients. In addition, HER-2 (+) → (-) patients had a poor DFS in the meta-analysis. However, there was no statistically significant difference in HER-2 (+) → (-) patients in terms of the OS. A retrospective analysis (11) involved 182 advanced breast cancer patients with HER-2 (+) → (-) at the metastatic site. There were significant differences between HER-2 (+)→ (-) and HER-2 (+) → (+) patients in terms of the OS, irrespective of whether patients were given trastuzumab or not. However, in the HER-2 (+) → (-) subgroup, the OS did not differ between those receiving trastuzumab and those who did not. These results suggest that patients with loss of HER-2 status may be less sensitive to trastuzumab. Previous research suggested that receptor changes were indicators of poor prognosis for both residual (29, 30) and metastatic sites (18, 31, 32). In our study, the survival analysis of patients showed no relationship between ER, PR, HER-2 receptor changes and survival. However on subgroup analysis of patients undergoing ER and PR status change those patients in the ER (+) → (-) and PR (+) → (-) patients had significantly shorter survival, which is consistent with earlier reports.

In conclusion, these results suggest there is a need for reassessment of ER, PR and HER-2 status in surgical samples from patients following NAC, and that NAC-induced changes in the HR state may be used as a prognostic factor.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of İzmir Bozyaka Training and Research Hospital (decision date and number: 24.11.2021-2021/191).

Informed Consent: It is a retrospective observational study and there is no informed consent form.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Z.; Concept: Ö.Ö.; Design: Ö.Ö., B.Z.; Data Collection and/or Processing: B.Z., D.K.Ç., C.Y.; Analysis and/or Interpretation: R.D., Literature Search: Ö.Ö., B.Z., D.K.Ç.; Writing: Ö.Ö., B.Z.

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

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

References

1. Rouzier R, Perou CM, Symmans WF, Ibrahim N, Cristofanilli M, Anderson K, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res 2005; 11: 5678-5685. (PMID: 16115903) [Crossref]
2. Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. J Clin Oncol 2010; 28: 92-98. (PMID: 19933921) [Crossref]
3. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist 2009; 14: 320-368. (PMID: 19346299) [Crossref]
4. Esserman LJ, Berry DA, DeMichele A, Carey L, Davis SE, Buxton M, et al. Pathologic complete response predicts recurrence-free survival more effectively by cancer subset: results from the I-SPY 1 TRIAL--CALGB 150007/150012, ACRIN 6657. J Clin Oncol 2012; 30: 3242-3249. (PMID: 22649152) [Crossref]
5. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 2007; 13: 2329-2334. (PMID: 17438091) [Crossref]
6. Arun B, Bayraktar S, Liu DD, Gutierrez Barrera AM, Atchley D, Pusztai L, et al. Response to neoadjuvant systemic therapy for breast cancer in BRCA mutation carriers and noncarriers: a single-institution experience. J Clin Oncol 2011; 29: 3739-3746. (PMID: 21900106) [Crossref]

7. Faneyte IF, Schrama JG, Peterse JL, Remijnse PL, Rodenhuis S, van de Vijver MJ. Breast cancer response to neoadjuvant chemotherapy: predictive markers and relation with outcome. Br J Cancer 2003; 88: 406-412. (PMID: 12569384) [Crossref]
8. Guarneri V, Broglio K, Kau SW, Cristofanilli M, Buzdar AU, Valero V, et al. Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. J Clin Oncol 2006; 24: 1037-1044. (PMID: 16505422) [Crossref]
9. Lippman ME, Allegra JC, Thompson EB, Simon R, Barlock A, Green L, et al. The relation between estrogen receptors and response rate to cytotoxic chemotherapy in metastatic breast cancer. N Engl J Med 1978; 298: 1223-1228. (PMID: 651963) [Crossref]
10. Mamounas EP. NSABP Protocol B-27. Preoperative doxorubicin plus cyclophosphamide followed by preoperative or postoperative docetaxel. Oncology (Williston Park) 1997; 11(6 Suppl 6): 37-40. (PMID: 9213327) [Crossref]
11. Houssami N, Macaskill P, von Minckwitz G, Marinovich ML, Mamounas E. Meta-analysis of the association of breast cancer subtype and pathologic complete response to neoadjuvant chemotherapy. Eur J Cancer 2012; 48: 3342-3354. (PMID: 22766518) [Crossref]
12. Morris DM, Edwards J, Gelder F. Hormonal receptors in locally advanced breast cancer: change with response to neoadjuvant chemotherapy? J Surg Oncol 1991; 46: 156-158. (PMID: 2011025) [Crossref]
13. Hirata T, Shimizu C, Yonemori K, Hirakawa A, Kouno T, Tamura K, et al. Change in the hormone receptor status following administration of neoadjuvant chemotherapy and its impact on the long-term outcome in patients with primary breast cancer. Br J Cancer 2009; 101: 1529-1536. (PMID: 19809429) [Crossref]
14. Neubauer H, Gall C, Vogel U, Hornung R, Wallwiener D, Solomayer E, et al. Changes in tumour biological markers during primary systemic chemotherapy (PST). Anticancer Res 2008; 28: 1797-1804. (PMID: 18630463) [Crossref]
15. Howell SJ, Wardley AM, Armstrong AC. Re: Ki67 Index, HER2 Status, and Prognosis of Patients With Luminal B Breast Cancer. J Natl Cancer Inst 2009; 101: 1730-1731. (PMID: 19893007) [Crossref]
16. van de Ven S, Smit VT, Dekker TJ, Nortier JW, Kroep JR. Discordances in ER, PR and HER2 receptors after neoadjuvant chemotherapy in breast cancer. Cancer Treat Rev 2011; 37: 422-430. (PMID: 21177040) [Crossref]
17. Zhang N, Moran MS, Huo Q, Haffty BG, Yang Q. The hormonal receptor status in breast cancer can be altered by neoadjuvant chemotherapy: a meta-analysis. Cancer Invest 2011; 29: 594-598. (PMID: 22011281) [Crossref]
18. Niikura N, Liu J, Hayashi N, Mittendorf EA, Gong Y, Palla SL, et al. Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. J Clin Oncol 2012; 30: 593-599. (PMID: 22124109) [Crossref]
19. Jin X, Jiang YZ, Chen S, Yu KD, Shao ZM, Di GH. Prognostic value of receptor conversion after neoadjuvant chemotherapy in breast cancer patients: a prospective observational study. Oncotarget 2015; 6: 9600-9611. PMID: 25826079 [Crossref]
20. Tacca O, Penault-Llorca F, Abrial C, Mouret-Reynier MA, Raoelfils I, Durando X, et al. Changes in and prognostic value of hormone receptor status in a series of operable breast cancer patients treated with neoadjuvant chemotherapy. Oncologist 2007; 12: 636-643. (PMID: 17602055) [Crossref]
21. Burcombe RJ, Makris A, Richman PI, Daley FM, Noble S, Pittam M, et al. Evaluation of ER, PgR, HER-2 and Ki-67 as predictors of response to neoadjuvant anthracycline chemotherapy for operable breast cancer. Br J Cancer 2005; 92: 147-155. (PMID: 15611798) [Crossref]
22. Koda M, Sulkowska M, Kanczuga-Koda L, Tomaszewski J, Kucharczuk W, Lesniewicz T, et al. The effect of chemotherapy on Ki-67, Bcl-2 and Bak expression in primary tumors and lymph node metastases of breast cancer. Oncol Rep 2007; 18: 113-119. (PMID: 17549355) [Crossref]
23. Dede DS, Gumuskaya B, Guler G, Onat D, Altundag K, Ozisik Y. Evaluation of changes of biologic markers ER, PR, HER 2 and Ki-67 in breast cancer with administration of neoadjuvant dosedense doxorubicin, cyclophosphamide followed by paclitaxel. J BUON 2013; 18: 366-371. (PMID: 23818347) [Crossref]
24. Arens N, Bleyl U, Hildenbrand R. HER2/neu, p53, Ki67, and hormone receptors do not change during neoadjuvant chemotherapy in breast cancer. Virchows Arch 2005; 446: 489-496. (PMID: 15838646) [Crossref]
25. Tiezzi DG, Andrade JM, Ribeiro-Silva A, Zola FE, Marana HR, Tiezzi MG. HER-2, p53, p21 and hormonal receptors proteins expression as predictive factors of response and prognosis in locally advanced breast cancer treated with neoadjuvant docetaxel plus epirubicin combination. BMC Cancer 2007; 7: 36. (PMID: 17324279) [Crossref]
26. Zhao J, Wu YL, Wang YD, Zhao GR, Wang J. [Effects of neoadjuvant chemotherapy on estrogen and progesterone receptors and HER-2 in breast cancer]. Di Yi Jun Yi Da Xue Xue Bao 2004; 24: 1437-14399. (PMID: 15604081) [Crossref]
27. Li C, Fan H, Xiang Q, Xu L, Zhang Z, Liu Q, et al. Prognostic value of receptor status conversion following neoadjuvant chemotherapy in breast cancer patients: a systematic review and meta analysis. Breast Cancer Res Treat 2019; 178: 497-504. (PMID: 31471838) [Crossref]
28. Wu JY, Chen WG, Chen XS, Huang O, He JR, Zhu L, et al. Long-term outcomes following adjuvant endocrine therapy in breast cancer patients with a positive-to-negative change of hormone receptor status following neoadjuvant chemotherapy. Mol Clin Oncol 2014; 2: 997-1002. (PMID: 25279188) [Crossref]
29. Tan QX, Qin QH, Yang WP, Lian B, Wei CY. Prognostic value of hormone receptor status conversion following neoadjuvant chemotherapy in a series of operable breast cancer patients. Int J Clin Exp Pathol 2014; 7: 4086-4094. (PMID: 25120787) [Crossref]
30. Lim SK, Lee MH, Park IH, You JY, Nam BH, Kim BN, et al. Impact of molecular subtype conversion of breast cancers after neoadjuvant chemotherapy on clinical outcome. Cancer Res Treat 2016; 48: 133-141. (PMID: 25865655) [Crossref]
31. Lower EE, Khan S, Kennedy D, Baughman RP. Discordance of the estrogen receptor and HER-2/neu in breast cancer from primary lesion to first and second metastatic site. Breast Cancer (Dove Med Press) 2017; 9: 515-520. (PMID: 28814897) [Crossref]
32. Lindström LS, Karlsson E, Wilking UM, Johansson U, Hartman J, Lidbrink EK, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol 2012; 30: 2601-2608. (PMID: 22711854) [Crossref]

Original Article

Eur J Breast Health 2022; 18(2): 172-181
DOI: 10.4274/ejbh.galenos.2022.2021-9-4

Digital Mammography, Ultrasound and Magnetic Resonance Imaging Characteristics in Differential Diagnosis of Papillary Carcinoma Subtypes of the Breast and Diagnostic Challenges

Tuğba İlkem Kurtoğlu Özçağlayan[1], Meltem Öznur[2]

[1]Department of Radiology, Liv Hospital Vadistanbul, İstanbul, Turkey
[2]Department of Pathology, Tekirdağ Namık Kemal University School of Medicine, Tekirdağ, Turkey

ABSTRACT

Objective: We aimed to investigate mammography (MG), ultrasound (US), and magnetic resonance imaging (MRI) findings of papillary breast carcinoma subtypes and to compare the diagnostic features and performance of the imaging method in distinguishing subtypes.

Materials and Methods: Forty-two patients presenting with pathological diagnosis of 45 papillary carcinoma lesions, between 2014 and 2019, were included. Cases were assigned to five subgroups according to the latest World Health Organization (WHO) classification. The clinical characteristics (n = 45) and imaging features of each pathological subgroup were retrospectively related to imaging findings from US (n = 45), MG (n = 37), and breast MRI (n = 23), and further compared.

Results: The finding of a palpable mass in all subgroups was more common than nipple discharge on clinical breast evaluation, and no significant difference was found between the subgroups. Irregular shape on MG (10/12, 83.3%, p = 0.039) and US (11/12, 91.7%, p = 0.039) was found more frequently in invasive micropapillary carcinoma (IMPC) compared to other subgroups. Circumscribed margins (4/5, 80%, p = 0.002) occurred more frequently in papillary ductal carcinoma *in situ* (pDCIS) and encapsulated papillary carcinoma (EPC) than in other subgroups (6/8, 75%, p = 0.002). Lower apparent diffusion coefficient (ADC) values were found in solid papillary cancer (SPC) than in other subgroups (ADC = 0.35 x 10^{-3}, p = 0.017).

Conclusion: Radiological findings of papillary carcinomas overlap with each other. US and MRI are complementary when revealing specific morphological characteristics.

Keywords: Breast; cancer; magnetic resonance imaging; mammography; ultrasound

Cite this article as: Kurtoğlu Özçağlayan Tİ, Öznur M. Digital Mammography, Ultrasound and Magnetic Resonance Imaging Characteristics in Differential Diagnosis of Papillary Carcinoma Subtypes of the Breast and Diagnostic Challenges. Eur J Breast Health 2022; 18(2): 172-181

Key Points

- Due to their varying malignant potential, and nonspecific findings on imaging and histopathology, it is important to identify specific radiological findings in the differential diagnosis of papillary lesions.
- Ultrasound (US) and magnetic resonance imaging (MRI) were better at revealing the morphological characteristics of papillary lesions than mammography (MG). Furthermore, MRI was more useful than MG and US in showing the local spread of lesions and accompanying synchronous tumors.
- Both solid papillary carcinoma and encapsulated papillary carcinoma without invasive focus might be observed as oval or round well-circumscribed lesions on MG and can often be evaluated as BI-RADS 3 lesions
- Papillary neoplasms on MRI are similar to other invasive breast cancers in enhancement kinetics and diffusion restriction properties.

Corresponding Author:
Tuğba İlkem Kurtoğlu Özçağlayan; drtugbailkem@yahoo.com

Received: 15.09.2021
Accepted: 07.03.2022
Available Online Date: 01.04.2022

Introduction

Papillary lesions of the breast are a group of proliferative diseases with solid components, typically cystic in nature and characterized by florid epithelial hyperplasia, originating from the ducto-lobular system (1, 2). Papillary carcinomas constitute less than 2% of all breast carcinomas (3) and the vast majority is seen in postmenopausal women (4). The intraductal papillary neoplasms of the breast include papilloma, papilloma with atypical ductal hyperplasia or ductal carcinoma *in situ* (DCIS), papillary DCIS (pDCIS), encapsulated papillary carcinoma (EPC), solid papillary carcinoma (SPC) and invasive papillary carcinoma (IPC) (5, 6). Invasive micropapillary carcinoma (IMPC) entity is listed under the invasive breast carcinoma category in the latest World Health Organization (WHO) classification of breast tumors (7).

Due to their varying malignant potential, and nonspecific findings on imaging and histopathology, papillary lesions present significant diagnostic and treatment challenges for radiologists, pathologists, and surgeons. The possibility of a high-risk lesion and neoplasia after excision of lesions shown to be benign papillomas by core biopsy has been demonstrated in previous studies (8). This situation has made it more important to reveal specific radiological findings in the differential diagnosis of papillary lesions.

There are publications about the contribution of imaging findings in the differentiation of benign and malignant papillary lesions (8, 9). However, there is a limited number of articles that examine all malignant papillary lesions subtypes and report their distinctive features from each other. In this large group of benign, in-situ, and invasive lesions, it is important to define the diagnostic radiological features of the lesions from each other, to indicate the correct surgical approach in the treatment of these lesions, and to prevent inadequate or excessive surgical treatments.

In this comprehensive study, we retrospectively examined the clinical and imaging findings of subtypes of malignant papillary lesions according to the current WHO classification. We aimed to investigate the differences between ultrasound (US), mammography (MG), and magnetic resonance imaging (MRI) findings in papillary breast cancers and to compare the advantages and disadvantages of imaging methods in distinguishing subtypes.

Materials and Methods

Patients and Histopathology

This study was conducted with the approval of the local ethics committee (approval number: 2019.119.07.15) dated 06/27/2019. Informed consent was obtained from all patients included in the study. Patients with papillary lesions diagnosed by histopathology at Tekirdağ Namık Kemal University School of Medicine Education and Research Hospital between 2014–2019 were obtained from the hospital patient data base management system. Hematoxylin&Eosin and Immunohistochemically stained slides of these patients were taken from the pathology archive and re-evaluated by a histopathologist with more than ten years experience. Case diagnosis was updated according to the latest WHO classification (WHO classification of tumors, 2019, 5th edition) (7). According to this classification, patients diagnosed with intraductal papilloma were excluded from the study. Patients with pDCIS, EPC, IPC, SPC (for both *in situ* and invasive), and IMPC under the heading of papillary neoplasms were included in the study. There were two separate (EPC and SPC) lesions in one case. There were also three separate (one IMPC and two separate EPC) lesions in another case. There was co-existence of EPC and invasive ductal carcinoma (IDC) in two cases. As a result, 42 patients and 45 lesions with preoperative imaging findings were included in the study.

Clinical Features

Patient demographic and clinical characteristics, such as age, lesion location, palpable lesion, and nipple discharge, were recorded. Lesions with a distance of less than 3 cm to the nipple were classified as central, and those with a distance of 3 cm or more were classified as peripheral. Lesion size was evaluated according to the largest diameter measured on MRI, mammography, or US images. Axillary lymph node involvement was recorded according to postoperative pathology results.

Imaging Techniques

Thirty-seven out of 42 patients had MG, 42/42 had US, and 23/42 had MRI examinations, respectively. MG examinations were obtained using the Selenia™ Dimensions Mammography System (Hologic™, USA) device. MGs were examined in two standard projections, craniocaudal and medio lateral oblique. US was performed by the same radiologist in an unblinded setting with the Toshiba™ Applio™ XG device, using a 6–12 MHz linear transducer. All MRI examinations were obtained using a 1.5-T, whole-body, MRI scanner (BRIVO MR 355, GE™ Healthcare™, USA) device with an eight-channel breast coil.

With the examination performed in the prone position, the MRI protocol was as follows: Axial T2W fat-saturated image time of repetition (TR) 5,490 ms, time of echos (TE) 85 ms, slice thickness 5 mm, and matrix 320 x 256. T1W Spoiled Gradient Echo (SPGR) was also used with the settings: TR/TE: 4.8 ms/2.2 msn, slice thickness 2 mm, matrix 360 x 360 x 128. Gadoteric acid (Dotarem™, Guerbet™) was administered at a dose of 0.1 mmol/kg at a rate of 2 mL/sec, followed by administration of 20 mL/sec saline for 6 times for contrast-enhanced MRI images. The first acquisition started at 25 seconds after contrast injection. Imaging parameters of diffusion-weighted imaging (DWI) with b = 1,000 s/mm^2 value of the breast were TR/TE 6,050/84.3 ms, slice thickness/slice spacing was 5 mm/1 mm, field-of-view was 30 x 32 cm, and reconstruction matrix of 256 x 256.

Imaging Interpretation

All radiological images were evaluated retrospectively by the same radiologist with ten years of experience. Imaging findings from US, MG, and MRI were evaluated using the latest atlas of the American College of Radiology Breast Imaging Reporting and Data System (ACR-BI-RADS 2013). On MG, the visibility of the lesion was evaluated initially. Breast composition BI-RADS final assessment categories were recorded. According to the categories in the ACR BI-RADS atlas, lesion characteristics (mass, asymmetry, calcification), shape of mass (oval, round, or irregular), margin of mass (circumscribed, obscured, microlobulated, indistinct, or spiculated), density of mass (compared to fat, low, equal, or high) and associated features (skin retraction, nipple retraction, skin thickness, or architectural distortion) were evaluated. Calcifications were evaluated according to morphology and distribution characteristics. US features were assessed for mass (shape, margin, orientation, echo pattern, or posterior features) and associated features (ductal changes, or vascularity).

MRI findings were examined in two groups, divided into those with mass enhancement and non-mass enhancement. Cases with both mass

lesions and non-mass enhancement were included in both categories. Non-mass enhancements were evaluated according to their distribution and enhancement pattern. Ductal ectasia was evaluated as ductal high signal intensities in precontrast T1W images on MRI examinations or dilated ductus in the US image. The kinetic enhancement curve was evaluated in dynamic contrast series. Apparent diffusion coefficient (ADC) values were measured and recorded in DWI sequences.

Statistical Analysis

Data analysis was performed using IBM SPSS, version 17.0 (IBM Inc., Armonk, NY, USA). Shapiro–Wilk test was used to determine whether the distributions of continuous variables were normal or not. The assumption of homogeneity of variances was examined by the Levene test. Descriptive statistics were expressed as mean ± standard deviation, median (25^{th}–75^{th}) percentiles or the number of cases, and (%), where appropriate. While the differences in BI-RADS, maximum lesion size, and DWI values among subgroups were compared by using Kruskal-Wallis test, a one-way ANOVA test was applied for the comparison of age levels. A chi-square test was used for categorical variables. If the expected number of categorical variables in any group was less than 5, the Fischer test *p*-value was accepted. $p<0.05$ was considered statistically significant.

Results

Two of the patients were men and 40 were women. One of the male cases was diagnosed with pDCIS and the other with EPC. Descriptive characteristics and clinical findings of the cases are shown in Table 1. There was no statistical difference in the papillary cancer subgroups in terms of previous history of breast cancer, BI-RADS classifications of

Table 1. Descriptive characteristics of study population

	Papillary DCIS (n = 5)	Encapsulated (cystic) papillary ca (n = 8)	Solid papillary (n = 7)	Invasive papillary (n = 13)	Invasive micropapillary (n = 12)	*p*-value
Mean age (years)	62.2±19.9	62.9±10.6	56.6±10.3	62.7±13.4	60.4±8.2	0.835†
Gender						
Male	1 (20.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.202‡
Female	4 (80.0%)	7 (87.5%)	7 (100.0%)	13 (100.0%)	12 (100.0%)	
Previous breast ca	1 (20.0%)	3 (37.5%)	2 (28.6%)	1 (7.7%)	0 (0.0%)	0.138‡
Palpation	5 (100.0%)	6 (75.0%)	7 (100.0%)	11 (84.6%)	7 (58.3%)	0.146‡
Nipple discharge	1 (20.0%)	4 (50.0%)a	0 (0.0%)	1 (7.7%)a	1 (8.3%)	**0.044‡**
BI-RADS						
0	0 (0.0%)	3 (37.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.217¶
3	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
4a	1 (20.0%)	0 (0.0%)	0 (0.0%)	3 (23.1%)	1 (8.3%)	
4b	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (15.4%)	0 (0.0%)	
4c	1 (20.0%)	1 (12.5%)	2 (28.6%)	1 (7.7%)	1 (8.3%)	
5	2 (40.0%)	4 (50.0%)	5 (71.4%)	7 (53.8%)	10 (83.3%)	
Breast composition						
A	0 (0.0%)	2 (28.6%)	1 (14.3%)	2 (15.4%)	0 (0.0%)	0.352‡
B	2 (50.0%)	3 (42.9%)	5 (71.4%)	10 (76.9%)	9 (75.0%)	
C	2 (50.0%)	1 (14.3%)	1 (14.3%)	1 (7.7%)	3 (25.0%)	
D	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Lesion side						
Left	3 (60.0%)	5 (62.5%)	3 (42.9%)	6 (46.2%)	6 (50.0%)	0.939‡
Right	2 (40.0%)	3 (37.5%)	4 (57.1%)	7 (53.8%)	6 (50.0%)	
Location						
Central	3 (60.0%)	6 (75.0%)	5 (71.4%)	4 (30.8%)	6 (50.0%)	0.285‡
Peripheral	2 (40.0%)	2 (25.0%)	2 (28.6%)	9 (69.2%)	6 (50.0%)	
Maximum diameter	52.0 (18.5–70.0)	29.5 (19.0–34.7)	22.0 (17.0–26.0)	23.0 (14.5–37.5)	17.5 (10.7–23.5)	0.160¶
Axillary lymphadenopathy	**-**	**3 (75.0%)**	**1 (16.7%)**	**3 (60.0%)**	**3 (50.0%)**	**0.521†**

Significant values are shown in bold.

Data are shown as mean ± SD, median (25^{th}–75^{th} percentiles) and n (%). †One-Way ANOVA, ‡Fisher-Freeman Holton test, ¶Kruskal-Wallis test, [a]: Encapsulated papillary Ca vs. invasive papillary Ca (p = 0.047).

BI-RADS: Breast Imaging Reporting and Data System; DCIS: ductal carcinoma *in situ;* ca: carcinoma; n: number; SD: standard deviation

lesions, breast composition, lesion side, lesion location, the maximum diameter of lesions, or axillary lymph node involvement (Table 1). Although the finding of a palpable mass in all subgroups was more common than nipple discharge on clinical breast evaluation, no significant difference was found between the subgroups (p> 0.05). There was a significant difference between the subgroups in terms of nipple discharge (p = 0.044) with the rate of nipple discharge being higher in the EPC subgroup (4/8, 50%) compared to the IPC subgroup (1/13, 7.7%, p = 0.047) (Table 1) although it is less common clinical finding among the subgroups.

Imaging Characteristics

In the study subgroup, lesions were detected in four of five cases in pDCIS, seven of eight cases in EPC, six of seven cases in SPC, eight of 13 cases in IPC, and 12 of 12 cases in IMPC on MG imaging. Lesions were occult in eight cases on MG imaging. When MG characteristics of the subgroups were compared with each other, lesions in the IMPC subgroup were frequently observed as irregularly shaped (Figure 1), while those in EPC subgroup were often found to be round or oval-shaped. There was a significant difference in IMPC subgroup in terms of frequency of occurrence of irregular shape (p = 0.039), and the rate of irregularities in IMPC subgroup was higher than in EPC subgroup (p = 0.006). There was a significant difference between the subgroups in terms of the frequency of margins being circumscribed or non-circumscribed (p = 0.017). The circumscribed rate was higher in pDCIS subgroup compared to that of the SPC and IMPC subgroups (p = 0.033 and p = 0.027, respectively). The ratio of circumscribed margin in the IMPC subgroup was also statistically significantly lower than in the EPC subgroup (p = 0.038). There was no statistical difference between subgroups in terms of calcification. Calcification was similarly observed in SPC (33.3%) and IMPC (33.3%), and it was amorphous or finely pleomorphic. There was no statistical difference between the subgroups for the presence of skin retraction, nipple retraction, architectural distortion, and other characteristics examined (p>0.05) (Table 2).

In comparison to their ultrasonographic features, there was a significant difference between the subgroups in terms of irregular shape (p = 0.039) with the rate of occurrence of irregularities in the IMPC subgroup being higher than in the EPC and SPC subgroups (p = 0.004 and p = 0.038, respectively). There was also a difference between the subgroups in respect of circumscribed margins (p = 0.002). The circumscribed margin rate was higher in the pDCIS subgroup compared to SPC and IMPC subgroups (p = 0.010 and p = 0.019, respectively). The circumscribed margin rate was significantly higher in the EPC subgroup than in the SPC and IMPC subgroups (p = 0.007 and p = 0.028, respectively) (Figure 2). A significant difference was also found between the subgroups in terms of the ratio of cystic/solid echopattern (p = 0.006), with this ratio being higher in the pDCIS and EPC subgroups compared to the SPC subgroup (p = 0.031 and p = 0.006, respectively) (Figure 3). There was no difference between subgroups as to other characteristics examined (p>0.05) (Table 3).

No statistical difference was observed for subgroup comparisons in respect of mass enhancement and non-mass enhancement (p = 0.682 and p = 0.964) on MRI. The distributions of non-enhancing findings, axillary lymphadenopathy, and kinetic curve assessment findings of the subgroups were similar (p>0.05). All lesions were slightly hyperintense on DWI, and ADC values ranged from 0.1 x 10^{-3} mm^2/s to 1.5 x 10^{-3} mm^2/s. There was a statistically significant difference in ADC levels between subgroups (p = 0.017), which was lower in the SPC subgroup compared to the IPC subgroup (p = 0.036) (Table 4).

Discussion and Conclusion

Our study demonstrated that there was no distinctive radiological imaging feature that distinguishes subgroups of papillary breast carcinomas, and papillary carcinomas may have imaging features similar to other invasive breast tumors. Papillary lesions should be

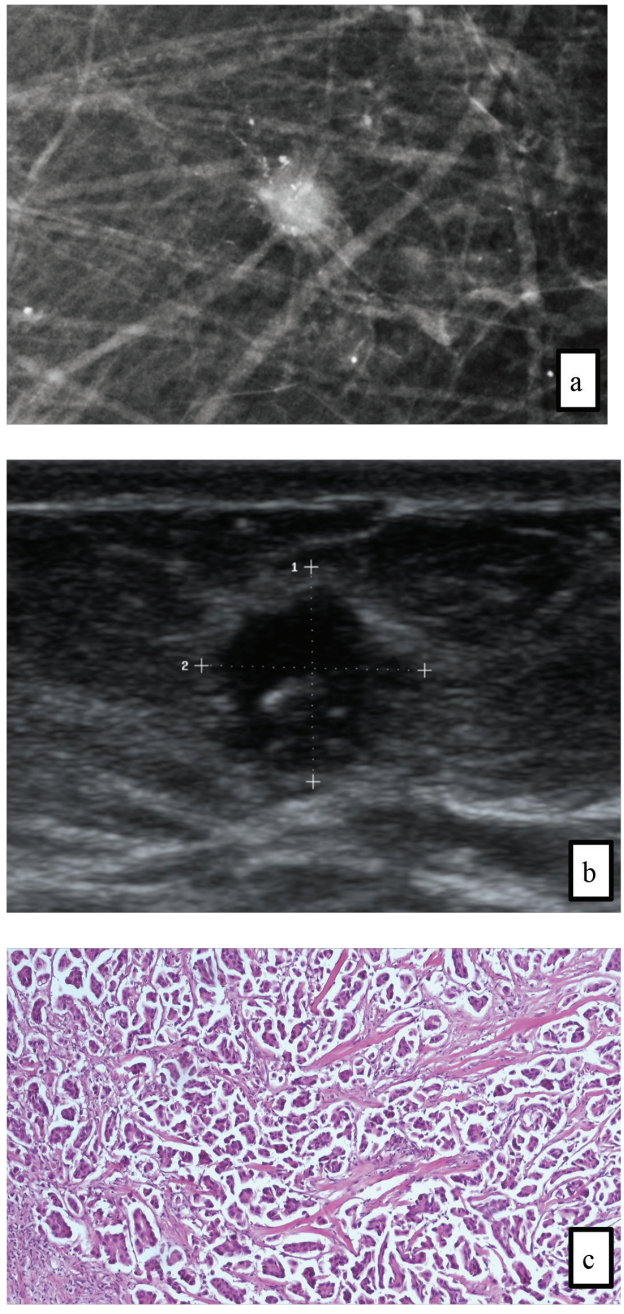

Figure 1. Invasive micropapillary carcinoma in 65-year old woman who underwent MG screening. **a)** A magnified cranio-caudal mammogram shows the irregular, high density mass with spiculated margins and pleomorphic microcalcifications. **b)** Gray scale US image shows the same lesion as hypoechoic mass with spiculated margins in the low inner quadrant. **c)** Photomicrography shows clusters of tumor cells in a micropapillary arrangement that appears to be within empty stromal spaces (H&E stain, x200).

MG: mammography; US: ultrasonography; H&E: hematoxylin & eosin

Table 2. Mammographic characteristics of study population

	Papillary DCIS (n = 4)	Encapsulated (cystic) papillary ca (n = 7)	Solid papillary (n = 6)	Invasive papillary (n = 8)	Invasive micropapillary (n = 12)	*p*-value
Shape of mass						
Oval	2 (50.0%)	4 (57.1%)	1 (16.7%)	5 (62.5%)	2 (16.7%)	0.155†
Round	0 (0.0%)	2 (28.6%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	0.170†
Irregular	2 (50.0%)	1(14.3%)[a]	4 (66.7%)	3 (37.5%)	10 (83.3%)[a]	**0.039†**
Margin of mass						
Circumscribed	3 (75.0%)[b,c]	4 (57.1%)[a]	0 (0.0%)[b]	3 (37.5%)	1 (8.3%)[a,c]	
Not circumscribed	1 (25.0%)[b,c]	3 (42.9%)[a]	6 (100.0%)[b]	5 (62.5%)	11 (91.7%)[a,c]	**0.017†**
Density of mass						
Equal	1 (25.0%)	2 (28.6%)	4 (66.7%)	4 (57.1%)	4 (33.3%)	0.524†
High	3 (75.0%)	5 (71.4%)	2 (33.3%)	3 (42.9%)	8 (66.7%)	
Asymmetry	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Calcifications	0 (0.0%)	0 (0.0%)	2 (33.3%)	0 (0.0%)	4 (33.3%)	
Morphology	0 (0.0%)	0 (0.0%)	2 amorphous	0 (0.0%)	2 amorphous	
					2 fine pleomorfic	0.104†
			2 (33.3%)		4 (33.3%)	
Distribution	0 (0.0%)	0 (0.0%)	2 grouped	0 (0.0%)	4 grouped	0.104†
Associated features						
Skin retraction	1 (25.0)	0 (0.0%)	3 (50.0%)	0 (0.0%)	1 (9.1%)	
Nipple retraction	2 (50.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Skin thickening	1 (25.0%)	1 (14.3%)	3 (50.0%)	1 (14.3%)	1 (9.1%)	0.573†
Architectural distortion	1 (25.0%)	2 (28.6%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	

Significant values are shown in bold.

Data are shown as n (%). †Fisher Freeman Holton test, [a]: Encapsulated papillary ca vs. invasive micropapillary ca (p<0.05), [b]: Papillary DCIS vs. solid papillary (p = 0.033), [c]: Papillary DCIS vs. invasive micropapillary (p = 0.027).

DCIS: ductal carcinoma in situ; ca: carcinoma; n: number

considered in the differential diagnosis if lesions show a morphological relation to duct structures and/or present as complex cystic and solid findings. Both US and MRI were better for revealing the morphological characteristics of papillary lesions than MG, and MRI was more useful than MG and US in showing the local spread of lesions and accompanying synchronous tumors.

Imaging findings of papillary lesions of the breast with benign or malignant breast lesions are various and can be confused radiologically. They can be seen as mass formation with smooth or irregular borders, as well as non-mass lesions with indistinct borders. Since lesions originate from ductal structures, their relationship with ductal structures may not always be demonstrated by imaging methods. Therefore, papillary lesions of the breast can be classified into different categories, ranging from BI-RADS 3 to BI-RADS 5.

In our study, all cases in subgroups occurred most frequently in the sixth decade. Among all subgroups, the youngest patient was diagnosed as IPC at the age of 34, and the oldest patient was in SPC (*in situ*) subgroup at the age of 90. There are several studies in the literature reporting that SPC maybe seen in the young patient group, and a few publications are reporting that SPC might also be seen in patients in their 20s (10, 11). There have been rare publications that report papillary lesions in male patients, such as a study done by Zhong et al. (12), which reported 117 male cases in a period of of 19 years. In our study, we had two male cases, one pDCIS, and one EPC.

Papillary lesions of the breast present as clinically palpable mass or nipple discharge. In our study, nipple discharge was most frequently observed in the EPC subgroup (50%). Nipple discharge has been seen less frequently with a rate of 0%–50% among all subgroups in our study. Bloody nipple discharge was reported in at least one-third of EPCs in the literature (13, 14). Although serous or bloody nipple discharge may occur in papillary carcinomas, in our cohort it was not a very common clinical finding. On the other hand, mass lesions palpated by clinical examination are more common in all subgroups and it was seen in 58%–100% of all groups in our study. Palpable mass findings were mostly observed in the SPC and the pDCIS subgroups. A clinically palpable mass lesion is usually related to the tumor diameter. The subgroup with the highest mean tumor diameter was pDCIS, and the subgroup with the lowest was the IMPC in our study. IMPC is a more aggressive tumor and may be associated with lymph node involvement, even in a smaller size, due to its lymphoproliferative nature. Lymph node involvement is frequently

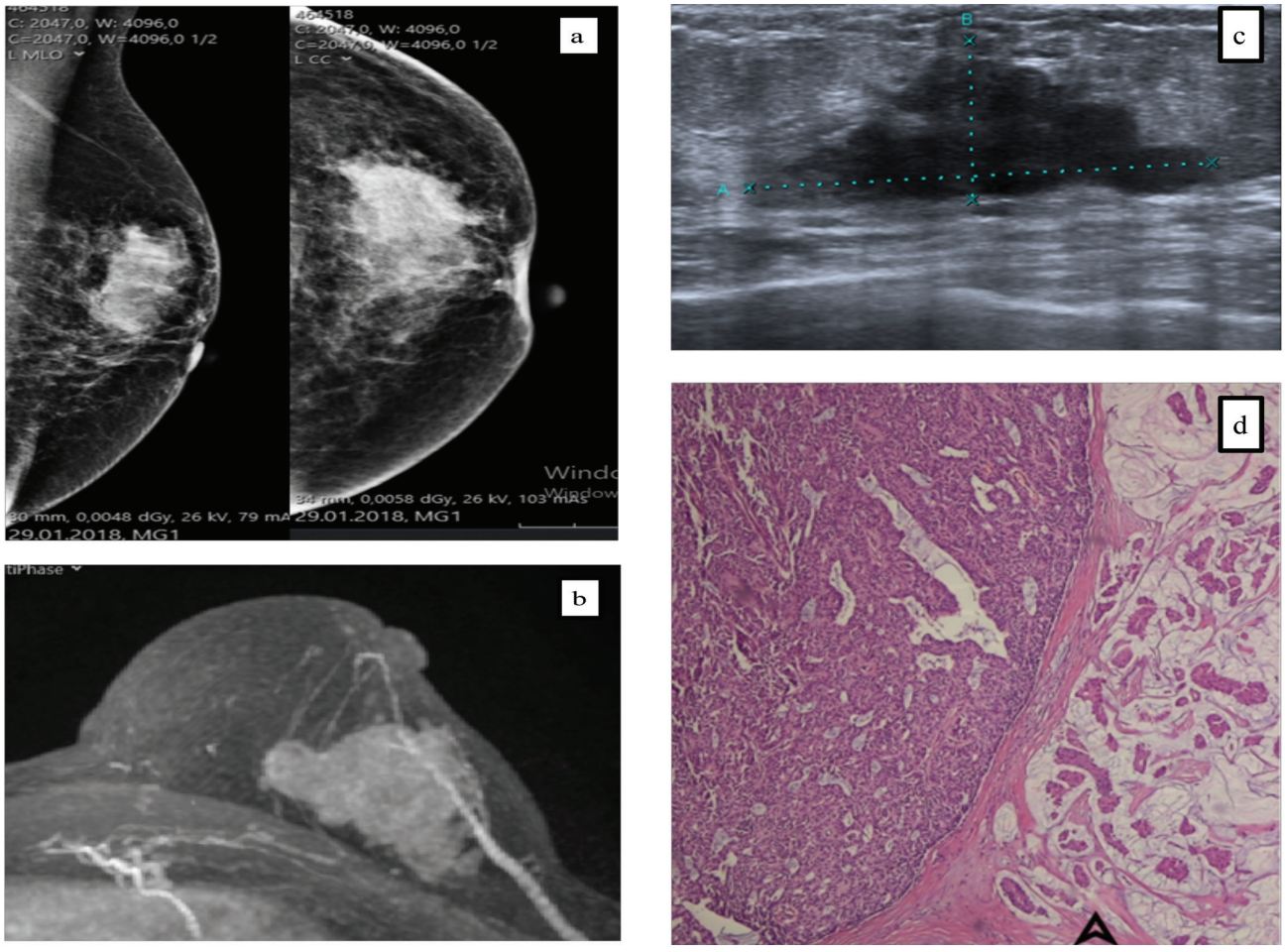

Figure 2. Solid papillary carcinoma in 65-year old woman who underwent MG screening. **a)** Mediolateral oblique and cranio-caudal MG shows irregular shaped dense mass in upper outer quadrant. **b)** Axial T1W SPGR contrast-enhanced 3D MRI image shows an irregular circumscribed mass with heterogenous enhancement. **c)** US image shows a hypoechoic mass with irregular borders. **d)** Photomicrograph shows the solid papillary carcinoma with a well-defined solid growth pattern, fibrovascular cores and monotonous population of ovoid to spindle-shaped epithelial cells with an invasive carcinoma component (arrowhead) (H&E stain, x200).

MG: mammography; MRI: magnetic resonance imaging; SPGR: spoiled gradient echo; US: ultrasonography; H&E: hematoxylin & eosin

present due to its significant lymphotrophic character at the time of initial diagnosis of IMPCs (13, 15). In many studies, axillary lymph node involvement has been reported, at rates ranging from 69%–95% (16, 17). Axillary lymph node involvement was present in only 50% of IMPC cases in our study.

In our study, locations of lesions were usually central, and no statistical difference was shown between subgroups, although the rate of central location was the highest in the EPC subgroup (75%). In parallel with our findings, a few publications showed that EPC was frequently centrally located and presented with a palpable mass in the retroareolar region (5, 18). We found that the IPC subgroup was the most peripheral subgroup (69.2%) among all subgroups and presented with a palpable mass. In the literature, half of the masses were reported to be centrally located and presented with a nipple discharge (13).

It is very difficult to differentiate papillary tumors by imaging methods, especially by MG. The percentage of occult lesions was 18% in MG. With a rate of 62% the subgroup with the highest rate of occult lesions was IPC. This finding may be explained because 21% of the study group had type C and type D breast density, and breast tissue superimposed over the lesions. Another reason was the difficulty in determining multiple foci with a segmental distribution using MG, which does not establish mass formation, especially in IPC cases. Our study showed that papillary carcinomas can be observed on MG as either circumscribed lesions with oval or lobulated contours or asymmetric densities. Although they are frequently observed as well-circumscribed masses, as reported in the literature, they may have indistinct margins. Microcalcifications were often amorphous and finely pleomorphic calcifications. There was no microcalcification in the pDCIS subgroup. However, linear, granular, or fixed calcification can be seen in pDCIS. We did not observe calcifications as an associated feature in EPC. Accompanying microcalcification in EPC has been rarely reported in the literature (19). Concomitant microcalcification on MG was rarely reported in the literature in SPC cases (20, 21), and 33.32% of SPC in our study were accompanied by amorphous calcifications. We found no mammographic microcalcification of IPC cases. However, Ciurea et al. (18) reported IPCs as round or lobulated masses, often associated with mammographic calcification. IMPC is a clinically aggressive variant of invasive carcinomas. IMPCs are irregular, spiculated, or indistinct, high-density masses on MG (15, 22). In our study,

IMPC was the most common mammographic mass formation and concomitant microcalcification was observed in 33.3% of the cases. In the literature, concomitant microcalcification has been reported in 48%–68% of IMPC cases (15, 22, 23). According to our findings, although both SPC and IMPCs were most commonly accompanied by microcalcification of the subgroups, no difference was found when compared with other subgroups. Papillary cancers often have similar mammographic features to other invasive breast tumors. Our study also showed that SPC and EPC without invasive focus might be observed as oval or round, well-circumscribed lesions on MG and can often be evaluated as BI-RADS 3 lesions. These oval, smooth-contoured lesions encountered in the sixth and seventh decades are observed to be higher density than the breast parenchyma and if they are growing during follow-up, they may have malignant character. For the differential diagnosis of papillary neoplasm, it may be useful to perform additional imaging modalities, such as US or MRI, in order to better reveal the morphological features.

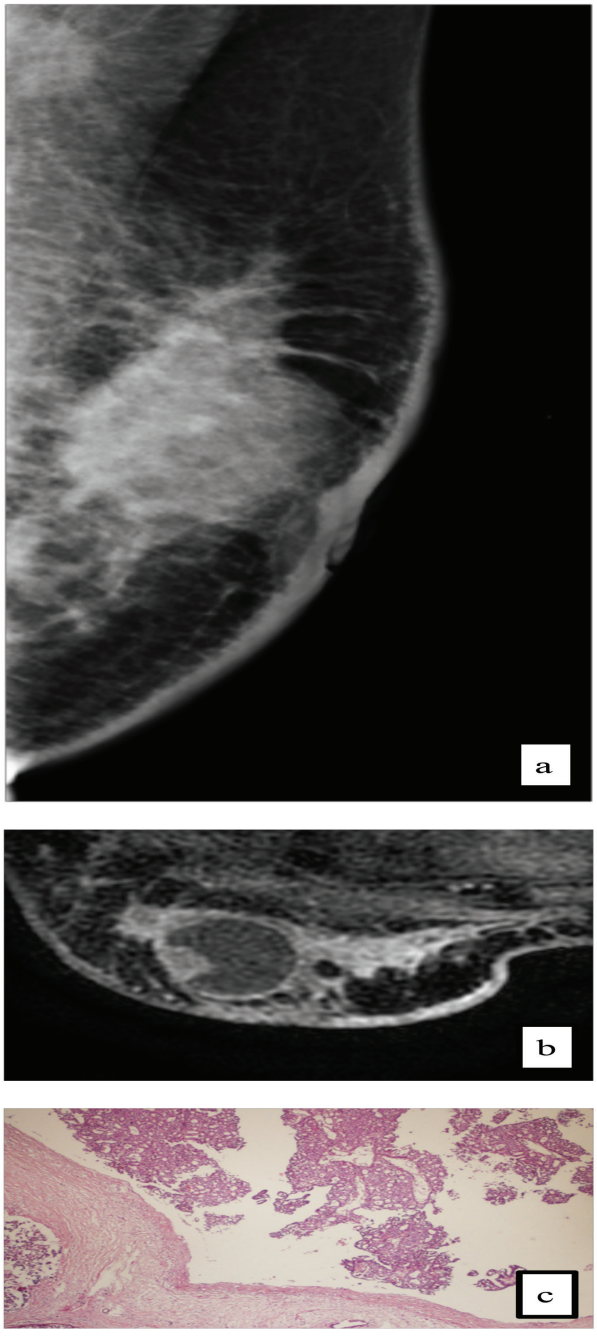

Figure 3. Encapsulated papillary carcinoma in a 50-year-old woman who presented with palpable lump. **a)** Mediolateral oblique mammogram shows the spiculated lesion with high density in the retroareolar location and associated axillary lymphadenopathy. **b)** Axial T1W contrast-enhanced MRI shows the complex cystic lesion with mural based nodule associated with invasive component at the posterolateral aspect of the lesion. **c)** Photomicrography shows the papillary proliferation, which consists of uniform cells surrounded by a fibrous capsule and does not contain myoepithelial cells (H&E stain, x100).

MRI: magnetic resonance imaging; H&E: hematoxylin & eosin

US is a very useful tool in the diagnosis of papillary lesions. In the further evaluation of a mass detected on MG, sonographic demonstration of cystic lesions with solid, or solid components associated with ductal structures, should bring to mind papillary lesions, and it is more useful than MG. However, the relation of papillary lesions originating from peripheral ducts with ductal structures may not always be demonstrated. It may appear similar to other invasive breast tumors, as in the examples of IPC and IMPC. EPCs have been ultrasonographically described in some previous studies as complex, cystic mass lesions with solid papillary projection originating from the cyst wall (24, 25). The typical complex, cystic appearance was present in 50% of our EPC cases. As stated in the literature, this typical appearance described on US and MRI examinations should bring EPC to mind in the differential diagnosis. However, it has been reported in the literature that this appearance may be similar to benign lesions, such as well-defined fibroadenoma and phyllodes tumor, as well as malignant lesions, including medullary or mucinous carcinoma (26). For this reason, it should be kept in mind that EPC can also appear as hypoechoic solid lesions. The increase in size and morphological changes in follow-up examinations, accompanying ductal extension and ductal dilatation should be considered for the possibility of malignancy in these lesions. pDCIS was observed as a complex, cystic-solid lesion in 40% of our cases. The imaging findings of SPC cases are also quite variable, and it has been reported sonographically as multiple nodules accompanied by ductal ectasia, well-circumscribed, complex, cystic lesion, and homogeneous solid lesions (10, 27, 28). In our study, SPC was observed as round, well-demarcated, or irregularly shaped lesios with microlobulated or spiculated margins. According to our experience, it can be seen as irregularly shaped of microlobulated or spiculated solid lesions, especially in subtypes with invasive components. In these cases, biopsy should be performed with the modality in which the lesion is best seen. In cases accompanied by calcifications, sampling calcifications with mammography would be an appropriate approach. In lesions with cystic and solid components, a cut biopsy can be performed from the solid component after aspiration of the cyst content. Sometimes, repeat biopsy may be necessary if the pathology is not consistent with imaging findings. At this stage, preferring biopsy methods where more tissue can be sampled, or excisional biopsy, will be a more appropriate approach, especially in papillary carcinoma cases.

MRI features of papillary neoplasms vary according to their subtypes. There are different imaging features of subgroups in the MRI range from mass to non-mass enhancement in dynamic contrast-enhanced series. The majority of our cases showed mass enhancement. While all of the SPCs and EPCs showed mass enhancement, pDCIS, SPC, and IMPC cases showed both mass and non-mass enhancement. Similar to US, MRI is valuable in the morphological evaluation of papillary

Table 3. Ultrasound characteristics of study population

	Papillary DCIS (n = 5)	Encapsulated (cystic) papillary ca (n = 8)	Solid papillary (n = 7)	Invasive papillary (n = 13)	Invasive micropapillary (n = 12)	p-value
Shape						
Oval	2 (40.0%)	3 (37.5%)	2 (28.6%)	6 (46.2%)	1 (8.3%)	0.348†
Round	0 (0.0%)	3 (37.5%)	2 (28.6%)	2 (15.4%)	0 (0.0%)	0.123†
Irregular	3 (60.0%)	2 (25.0%)[a]	3 (42.9%)[b]	7 (53.8%)	11 (91.7%)[a,b]	**0.039†**
Margin						
Circumscribed	4 (80.0%)[c,d]	6 (75.0%)[a,e]	0 (0.0%)[c,e]	4 (30.8%)	2 (16.7%)[a,d]	**0.002†**
Not circumscribed	1 (20.0%)[c,d]	2 (25.0%)[a,e]	7 (100.0%)[c,e]	9 (69.2%)	10 (83.3%)[a,d]	
Orientation						
Parallel	3 (60.0%)	4 (50.0%)	5 (71.4%)	9 (69.2%)	2 (16.7%)	0.068†
Not parallel	2 (40.0%)	4 (50.0%)	2 (28.6%)	4 (30.8%)	10 (83.3%)	
Echo pattern						
Isoechoic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Hypoechoic	3 (60.0%)	4 (50.0%)	7 (100.0%)	12 (92.3%)[f]	12 (100.0%)[a]	**0.006†**
Complex cystic/solid	2 (40.0%)	4 (50.0%)[a,f]	0 (0.0%)	1 (7.7%)	0 (0.0%)	
Posterior features						
No features	3 (60.0%)	6 (75.0%)	2 (28.6%)	8 (61.5%)	10 (83.3%)	
Posterior	2 (40.0%)	2 (25.0%)	5 (71.4%)	3 (23.0%)	2 (16.6%)	
Enhancement	0 (0.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.193†
Shadowing	2 (40.0%)	2 (25.0%)	2 (28.6%)	10 (77.0%)	10 (83.4%)	
Combined	1 (20.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Associated features	2 (40.0%)	2 (25.0%)	5 (71.4%)	2 (15.4%)	5 (41.7%)	
Duct changes	1 (20.0 %)	0 (0.0%)	2 (28.5%)	2 (15.4%)	2 (16.6%)	0.149†
Vascularity	2 (40.0%)	2 (25.0%)	5 (71.4%)	5 (38.4%)	4 (33.2%)	

Significant values are shown in bold.

Data are shown as n (%). †Fisher Freeman Holton test, [a]: Encapsulated papillary ca vs. invasive micropapillary (p<0.05), [b]: Solid papillary vs. invasive micropapillary (p = 0.038), [c]: Papillary DCIS vs. solid papillary (p = 0.010), [d]: Papillary DCIS vs. invasive micropapillary (p = 0.028), [e]: Encapsulated papillary ca vs. solid papillary (p = 0.007), [f]: Encapsulated papillary ca vs. invasive papillary (p = 0.047).

DCIS: ductal carcinoma *in situ*; ca: carcinoma; n: number

lesions and demonstrates their relationship with ductal structures. MRI has been useful in determining lesions, including pDCIS with a non-mass contrast enhancement pattern, that are mammographically occult and observed with indeterminate borders on US, and it shows typical morphological features of EPC cases with intracystic solid components. Besides morphological appearance, MRI plays a valuable role, especially in preoperative mapping, evaluation of local extension, and showing accompanying DCIS and invasive foci (29, 30). In one case from our study, there was co-existence of EPC and SPC and in one further case there were three separate lesions, one IMPC, and two separate EPC, while in two cases there was an association of EPC-invasive ductal carcinoma (IDC). We suggest that EPCs can be divided into *in situ* and invasive subgroups, like SPC.

Papillary neoplasms are similar to other invasive breast cancers in terms of enhancement kinetics and diffusion restriction properties. Similar to the literature, we found that papillary lesions often showed rapid enhancement kinetics in the early phase and wash out or plateau in the middle and late phases on dynamic contrast-enhanced imaging. There was no difference between subgroups in the case of contrast kinetics and diffusion features.

The limitations of our study were its retrospective design, an insufficient number of study patients which reflects the rarity of this uncommon tumor and heterogeneous subgroups, as well as lack of interobserver and intraobserver reliability testing.

In conclusion, subgroups of papillary carcinomas are extremely rare breast entities, presenting with radiological findings overlapping each other. US and MRI are more useful than mammography in revealing the relationship between the lesions and ductal structures. MRI is one step ahead of the other modalities in showing papillary lesions, and it is the most useful modality in preoperative evaluation. Although imaging findings do not reveal clear data in distinguishing these lesions, radiologists should carefully assess the clues that suggest papillary lesions in imaging findings and consider papillary lesions and subtypes in the differential diagnosis.

Table 4. Magnetic resonance characteristics of study population

	Papillary DCIS (n = 2)	Encapsulated (cystic) papillary ca (n = 4)	Solid papillary (n = 6)	Invasive papillary (n = 5)	Invasive micropapillary (n = 6)	*p*-value
MASS	**1 (50.0%)**	**4 (100.0%)**	**5 (83.3%)**	**5 (100.0%)**	**5 (83.3 %)**	
Shape						
Oval	-	1 (25.0%)	-	1 (20.0%)	-	
Round	-	3 (75.0%)	2 (33.3%)	1 (20.0%)	1 (16.6%)	
Irregular	1 (50.0%)	-	3 (50.0%)	3 (60.0%)	4 (66.6%)	
Margin						
Circumcribed	1 (50.0%)	4 (100.0%)	-	1 (20.0%)	-	
Non circumcribed	-	-	5 (83.3%)	4 (80.0%)	5 (83.3%)	
Internal enhancement						**0.682†**
Homogenous	-	-	1 (16.6%)	-	1 (16.6%)	
Heterogenous	1 (50.0%)	1 (25.0%)	4 (66.6%)	5 (100.0%)	4 (66.6%)	
Rim enhancement	-	3 (75.0%)	-	-	-	
Non MASS distribution	**1 (50.0%)**	**2 (50.0%)****	**2(33.3%)****	**3 (60.0%)****	**3 (50.0%)****	
Segmental	1 (50.0%)	-	-	-	1 (16.6%)	
Regional	-	-	1 (16.6%)	-	-	
Internal enhancement						**0.964†**
Homogenous	-	-	1 (16.6%)	-	1 (16.6%)	
Heterogenous	1 (50.0%)	-	5 (83.3%)	-	-	
Non enhancing findings	**0 (0.0%)**	**1 (25.0%)**	**3 (50.0%)**	**3 (60.0%)**	**0 (0.0%)**	**0.175†**
Kinetic curve assessment						
Persistent	-	-	-	-	-	
Plateau	1 (50.0%)	3 (75.0%)	3 (50.0%)	4 (80.0%)	5 (83.3%)	**0.796†**
Washout	1 (50.0%)	1 (25.0%)	3 (50.0%)	1 (20.0%)	1 (16.7%)	
DWI x 10^{-3}	**1.35 (1.30–1.40)**	**1.00 (0.37–1.17)**	**0.35 (0.10–0.90)[a]**	**1.10 (1.10–1.50)[a]**	**1.20 (0.90–1.50)**	**0.017‡**

Significant values are shown in bold.

Data are shown as median (25^{th}–75^{th} percentiles) and n (%). †Fisher Freeman Holton test, ‡ Kruskal-Wallis test, [a]:Solid papillary vs invasive papillary ($p = 0.036$).

** 2 cases in EPC subgroup, 1 case in SPC subgroup, 3 cases in IPC subgroup, 2 cases in IMPC subgroup showed both mass and non-mass enhancement.

DCIS: ductal carcinoma *in situ*; ca: carcinoma; EPC: encapsulated papillary carcinoma; IPC: invasive papillary carcinoma; DWI: diffusion-weighted imaging; n: number

Acknowledgments

The authors would like to thank Ömer Özçağlayan M.D., Assoc. Prof. Dr. and Sibel Özkan Gürdal M.D., Prof. Dr. for clinical and general support during this project.

Ethics Committee Approval: This study was approved by Tekirdağ Namık Kemal University Medical School Ethics Committee with "2019.119.07.15" approval number on 06.27.2019.

Informed Consent: Informed consent was obtained from all patients included in the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors declare that there is no conflict of interest regarding this manuscript.

Funding: All authors declare that no funding was received for this study.

Authorship Contributions

Surgical and Medical Practices: T.İ.K.Ö., M.Ö.; Concept: T.İ.K.Ö., M.Ö.; Design: T.İ.K.Ö., M.Ö.; Data Collection and/or Processing: T.İ.K.Ö., M.Ö.; Analysis and/or Interpretation: T.İ.K.Ö.; Literature Search: M.Ö.; Writing: T.İ.K.Ö.

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

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

References

1. O'Malley FP, Visscher D, MacGrogan G, Tan PH, Ichihara S. Intraductal papilloma. In: Lakhani S, Ellis I, Schnitt SJ, Tan PH, van de Vijver MJ, editors. WHO Classification of Tumours of the Breast. 4th ed. Lyon: IARC Press; 2012. p. 100-2. [Crossref]
2. Tan PH, Schnitt SJ, van de Vijver MJ, Ellis IO, Lakhani SR. Papillary and neuroendocrine breast lesions: the WHO stance. Histopathology 2015; 66: 761-770. (PMID: 24845113) [Crossref]
3. Mulligan AM, O'Malley FP. Papillary lesions of the breast: a review. Adv Anat Pathol 2007; 14: 108-119. (PMID: 17471117) [Crossref]
4. Liberman L, Feng TL, Susnik B. Case 35: Intracystic papillary carcinoma with invasion. Radiology 2001; 219: 781-784. (PMID:11376269) [Crossref]
5. Brogi E, Horii R, Mac Grogan G, et al. Papillary Neoplasms. Breast Tumours. WHO Classification of Tumours, 5th Edition, Volume 2 . WHO Classification of Tumours Editorial Board International Agency for Research on Cancer: Lyon; 2019. p. 49-67. [Crossref]
6. Tan PH, Ellis I, Allison K, Brogi E, Fox SB, Lakhani S, et al. The 2019 World Health Organization classification of tumours of the breast. Histopathology 2020; 77: 181-185. (PMID: 32056259) [Crossref]
7. Marchio C, Horlings HM, Vincent-Salomon A. Invasive Breast Carcinoma. Breast Tumours. WHO Classification of Tumours, 5th Edition, Volume 2 . WHO Classification of Tumours Editorial Board International Agency for Research on Cancer: Lyon; 2019. p. 128-130. [Crossref]
8. Jagmohan P, Pool FJ, Putti TC, Wong J. Papillary lesions of the breast: imaging findings and diagnostic challenges. Diagn Interv Radiol 2013; 19: 471-478. (PMID: 23996839) [Crossref]
9. Eiada R, Chong J, Kulkarini S, Goldberg F, Muradali D. Papillary lesions of the breast: MRI, ultrasound, and mamographic apperances. AJR Am J Roentgenol 2012; 198: 264-271. (PMID: 22268167) [Crossref]
10. You C, Peng W, Shen X, Zhi W, Yang W, Gu Y. Solid papillary carcinoma of breast: Magnetic resonance mamography, digital mammography, and ultrasound findings. J Comput Assist Tomogr 2018; 42: 771-775. (PMID: 29613993) [Crossref]
11. Nassar H, Qureshi H, Adsay NV, Visscher D. Clinicopathologic analysis of solid papillary carcinoma of the breast and associated invasive carcinomas. Am J Surg Pathol 2006; 30: 501-507. (PMID: 16625097) [Crossref]
12. Zhong E, Cheng E, Goldfischer M, Hoda SA. Papillary lesions of the male breast: A study of 117 cases and brief review of the literature demonstrate a broad clinicopathologic spectrum. Am J Surg Pathol 2020; 44: 68-76. (PMID: 31403965) [Crossref]
13. Karakas C, Resetkova E, Sahin AA. Papillary lesions of the breast. In: Palazzo JP, editor. Difficult Diagnoses in Breast pathology. Demos Medical Publishing; 2011. p. 56-87. [Crossref]
14. Rinaldi P, Ierardi C, Costantini M, Magno S, Giuliani M, Belli P, et al. Cyctic breast lesions. sonographic findings and clinical management. J Ultrasound Med 2010; 29: 1617-1626. (PMID: 20966473) [Crossref]
15. Günhan-Bilgen I, Zekioglu O, Ustün EE, Memis A, Erhan Y. Invasive micropapillary carcinoma of the breast: clinical, mammographic, and sonographic findings with histopathologic correlation. AJR Am J Roentgenol 2002; 179: 927-931. (PMID: 12239039) [Crossref]
16. Zekioglu O, Erhan Y, Ciris M, Bayramoglu H, Ozdemir N. Invasive micropapillary carcinoma of the breast: high incidence of lymph node metastasis with extranodal extension and its immunohistochemical profile compared with invasive ductal carcinoma. Histopathology 2004; 44: 18-23. (PMID: 14717664) [Crossref]
17. Kim MJ, Gong G, Joo HJ, Ahn SH, Ro JY. Immunohistochemical and clinicopathologic characteristics of invasive ductal carcinoma of breast with micropapillary carcinoma component. Arch Pathol Lab Med 2005; 129: 1277-1282. (PMID: 16196516) [Crossref]
18. Ciurea A, Calin A, Ciortea C, Dudea SM. Ultrasound in the diagnosis of papillary breast lesions. Med Ultrasound 2015; 17: 392-397. (PMID: 26343090) [Crossref]
19. Speer ME, Adrada BE, Arribas EM, Hess KR, Middleton LP, Whitman GJ. Imaging of intracystic papillary carcinoma. Curr Probl Diagn Radiol 2019; 48: 348-352. (PMID: 30072190) [Crossref]
20. Maluf HM, Koerner FC. Solid papillary carcinoma of the breast. A form of intraductal carcinoma with endocrine differentiation frequently associated with mucinous carcinoma. Am J Surg Pathol 1995; 19: 1237-1244. (PMID:7573685) [Crossref]
21. Tsang WY, Chan JK. Endocrin ductal carcinoma in situ (E-DCIS) of the breast: a form of low-grade DCIS with clinichopathologic and biologic characteristics. Am J Surg Pathol 1996; 20: 921-943. (PMID: 8712293) [Crossref]
22. Adrada B, Arribas E, Gilcrease M, Yang WT. Invasive micropapillary carcinoma of the Breast: Mamographic, sonographic and MRI features. AJR Am J Roentgenol 2009; 193: 58-63. (PMID: 19542384) [Crossref]
23. Yun SU, Choi BB, Shu KS, Kim SM, Seo YD, Lee JS, et al. Imaging findings of invasive micropapillary carcinoma of the breast. J Breast Cancer 2012; 15: 57-64. (PMID: 22493629) [Crossref]
24. Dogan BE, Whitman GJ, Middleton LP, Phelps M. Intracystic papillary carcinoma of the breast. AJR Am J Roentgenol 2003; 181: 186. (PMID: 12818855) [Crossref]
25. Yılmaz R, Cömert RG, Aliyev S, Toktaş Y, Önder S, Emirikçi S, et al. Encapsulated papillary carcinoma in a man with gynecomastia: ultrasonography, mammography and magnetic resonance imaging features with pathologic correlation. Eur J Breast Health 2018; 14: 127-131. (PMID: 29774323) [Crossref]
26. Muttarak M, Lerttumnongtum P, Chaiwun B, Peh WCG. Spectrum of papillary lesions of breast:clinical, imaging and pathologic correlation. AJR Am J Roentgenol 2008; 191: 700-707. (PMID: 18716096) [Crossref]
27. Lam WW, Chu WC, Tang AP, Tse G, Ma TK. Role of radiologic features in the management of papillary lesions of the breast. AJR Am J Roentgenol 2006; 186: 1322-1327. (PMID: 16632726) [Crossref]
28. Bazzocchi M, Berra I, Francescutti GE, Del Frate C, Zuiani C, Puglisi F, et al. Papillary lesione of the breast: diagnostic imaging and contribution of percutaneous needle biopsy with 14G needle. Radiol Med 2001; 101: 424-431. (PMID: 11479438) [Crossref]
29. Linda A, Zuiani C, Girometti R, Londero V, Machin P, Brondani G, et al. Unusual malignant tumors of the breast: MRI features and pathologic correlation. Eur J Radiol 2010; 75: 178-184. (PMID: 19446418) [Crossref]
30. Rodríguez MC, Secades AL, Angulo JM. Best cases from the AFIP: intracyctic papillary carcinoma of the breast. Radiographics 2010; 30: 2021-2027. (PMID: 21057133) [Crossref]

Original Article

Eur J Breast Health 2022; 18(2): 182-189
DOI: 10.4274/ejbh.galenos.2022.2021-11-8

Impact of Detection Mode in a Large Cohort of Women Taking Part in a Breast Screening Program

Marilina García[1,2,3,4], Maximino Redondo[1,2,3,4], Irene Zarcos[2,5], Javier Louro[2,6], Francisco Rivas-Ruiz[1,2], Teresa Téllez[2,3,4], Diego Pérez[5], Francisco Medina Cano[7], Kenza Machan[8], Laia Domingo[2,6], Maria del Mar Vernet[9], Maria Padilla-Ruiz[1,2], Xavier Castells[2,6], Maria Sala[2,6]

[1]Research Unit, Hospital Costa del Sol, Málaga, Spain
[2]Research Network on Health Services in Chronic Diseases (REDISSEC)
[3]Biomedical Research Institute of Málaga (Instituto de Investigación Biomédica de Málaga, IBIMA), Málaga, Spain
[4]Surgery, Biochemistry and Immunology Department, Medical School, University of Málaga, Málaga, Spain
[5]Department of Oncology, Hospital Costa del Sol, Marbella, Spain
[6]Department of Epidemiology and Evaluation, Hospital del Mar, Barcelona, Spain
[7]Department of Surgery, Hospital Costa del Sol, Marbella, Spain
[8]Department of Radiology, Hospital Costa del Sol, Marbella, Spain
[9]Department of Gynecology, Hospital del Mar, Barcelona, Spain

ABSTRACT

Objective: The aim of this study was to evaluate the existing survival rate and clinical-pathological differences among patients with breast cancer detected by mammographic screening.

Materials and Methods: This multicenter cohort study examined 1,248 patients who took part in a national screening program for the early detection of breast cancer over an eight-year period.

Results: Of the two patient subgroups (interval and screening), we found significant differences in the distribution of prognostic factors, with interval cases presenting at a lower mean age ($p = 0.002$), with higher percentages of human epidermal growth factor receptor 2 (HER-2) or triple negative and lower percentages of luminal A or luminal B carcinomas ($p = 0.001$), advanced stages ($p<0.001$), lower hormone receptor expression ($p<0.001$), poorer differentiation ($p<0.001$) and lower survival ($p<0.001$). Among the screening group, patients with tumors detected during the first screening round had a significantly lower mean age ($p<0.001$), a lower frequency of comorbidities ($p = 0.038$) and a lower tendency ($p<0.1$) to be diagnosed as triple negative breast carcinomas than incident cases.

Conclusion: Our results highlight that breast tumors detected during the first screening round are frequently characterized by a more benign phenotype than the rest of the screening subgroups, which could be of help when stratifying the risk of death and selecting the best treatment option for each patient.

Keywords: Breast cancer; risk factors; screening; survival

Cite this article as: García M, Redondo M, Zarcos I, Louro J, Rivas-Ruiz F, Téllez T, Pérez D, Cano FM, Machan K, Domingo L, Mar Vernet M, Padilla-Ruiz M, Castells X, Sala M. Impact of Detection Mode in a Large Cohort of Women Taking Part in a Breast Screening Program. Eur J Breast Health 2022; 18(2): 182-189

Key Points

- Death risk may be overestimated in breast cancer patients diagnosed by screening programs when the method of detection is not considered.
- Breast cancer screening subgroups present survival and clinical-pathological differences.
- Patient risk stratification according to the screening subgroup to which they belong (prevalent, interval, incident) can help optimize their clinical management and treatment.

Corresponding Author:
Maximino Redondo; mredondo@hcs.es

Received: 18.11.2021
Accepted: 03.03.2022
Available Online Date: 01.04.2022

Introduction

The World Health Organization (WHO) has declared cancer a leading cause of death worldwide, with an estimated 9.6 million deaths in 2018. Among the different cancer types, breast cancer caused 6.6% of worldwide cancer deaths in 2018, which represents the malignancy with higher incidence (24.2%, 32.825 new cases in Spain), mortality (15%) and 5-year prevalence (30.1%) rates among women worldwide (1).

According to the WHO, early detection is critical to improve breast cancer outcomes and survival. In this regard, despite selection, lead-time, length and overdiagnosis biases (2), the increasing implementation of screening programs has allowed for early patient diagnosis, quick treatment and an increased chance for successful treatment that can reduce mortality rates by up to 20% (3). For this reason, and despite reported handicaps of screening programs, such as high costs or derived risk from ionizing radiation, breast self-examination and other clinical explorations including mammography or ultrasonography represent the main tools for early diagnosis and timely treatment to lessen breast cancer morbidity. Indeed, although mammography screenings are not precise predictors of outcome (4) because of their inability to discriminate between malignant and benign breast masses, these programs along with histopathology studies have proven useful in significantly reducing mortality in women receiving adequate follow-up (5).

In some countries, breast cancer age-standardized mortality rates have decreased by 2%–4% per year since the 1990s, but others have yet to achieve this outcome, as countries with low breast cancer mortality rates are characterized by increased levels of essential health services coverage and higher numbers of public cancer centers (6). There is evidence that two thirds of all women with breast cancer are still diagnosed after presenting to their clinicians with symptoms and not through screening (7).

Contrary to these symptomatic tumors usually characterized by a fast development, growth and spread, breast screening normally detects a higher proportion of slow-growing tumors, that can even remain unnoticed in a woman's lifetime (4, 8-10), which are associated with a better prognosis than tumors of similar size found outside patient screening (11-14). In addition to differences in growth rate, the survival advantage of these cases may also be due to additional biological differences, such as hormone receptors expression or human epidermal growth factor receptor 2 (HER-2) status, among others (13, 15, 16). Studies also show agreement that screening-detected breast cancers have relatively better tumor prognostic characteristics, biomarker profile and survival outcomes than those tumors diagnosed between two screenings (17, 18), also known as interval tumors.

On the other hand, although the epidemiology, radiological and biological characteristics of interval breast cancers versus population mammography-detected screening tumors is well documented (17, 19, 20), the prognostic and biological differences between screening-detected breast cancer subtypes, namely prevalent tumors, when diagnosed in the first screening round, or incident tumors when diagnosed in successive screening rounds, still need to be clarified. In this regard, a previous study from our research group reported significant differences between prevalent and incident tumors, showing that prevalent breast tumor cases present more favorable biologic and prognostic features than incident cases (21).

Despite the potential clinical benefit that these biological and clinical-pathological differences could have when selecting the most appropriate treatment and care methods for breast cancer patients, they are not considered in common Clinical Practice Guidelines. For this reason, and as a continuation of our previous investigations, in the present study we will evaluate if there are sociodemographic, clinical and biologic differences between prevalent, incident and interval breast cancer cases and their association with patient overall survival in a large cohort of healthy Spanish women participating in breast cancer screening programs.

Materials and Methods

Study Design

We conducted an analytical study to evaluate the differences between breast cancer tumors detected during a screening test (prevalent and incident cases) and those detected in women after a negative screening test and before the next screening invitation (interval cases) (n = 1,086). We also evaluated the differences between prevalent and incident cases among screen-detected cases (n = 741). In addition, we performed a survival study to evaluate the impact of the detection process (screen-detected cancer vs. interval breast cancer) on global survival.

Patients and samples

This observational study included 1,086 women aged 45–69 years, with no known risk factors associated with breast cancer, who had participated in a screening program supported by four national breast-cancer screening programs which provide biannual mammograms and annual examinations for women with clinical indications of increased risk. This nationwide program meets the required standards (22). The diagnoses and surgical interventions all took place during the period 2000–2008, with follow up until 2014.

Variables

- Biologic characteristics: Phenotype (Luminal A, Luminal B, HER-2, Triple Negative), Stage (*in situ*, Stage I, Stage II, Stage III), Estrogen Receptor Expression (positive, negative), progesterone receptor expression (positive, negative), HER-2 receptor enrichment (positive, negative), Ki-67 score (<14%, >14%), tumor grade (Grade I, Grade II, Grade III), Death (yes, no).
- Patient clinical history: Associated diseases required to calculate the Charlston Comorbidity Index (CCI): myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, connective tissue pathology, ulcerative disease, mild/moderate/severe hepatic disease, diabetes, diabetes with organic lesion, hemiplegia, renal pathology (moderate/severe), solid neoplasms, leukemia, malignant lymphoma, solid metastasis, and/or AIDS.
- Survival.
- Patient: age, family history.

Scope

Data were obtained from the multicenter retrospective cohort of women CAMISS (ClinicalTrials.gov Identifier: NCT03165006) that included 1,086 women with breast cancer participating in a population-based screening program in which three public hospitals, belonging to the Spanish National Health Service, in three Spanish regions (Andalusia, Canary Islands, Catalonia) were involved. The main objective of the CAMISS-retrospective study was to evaluate the impact of the diagnosis process (screen-detected cancer vs. interval breast cancer) on overall survival (23).

Statistical Analysis

Univariate Analysis

Descriptive analysis segmented by the type of diagnosis (interval *versus* screening and prevalent *versus* incident). Comparison of the mean was performed by the Student's t-test after confirming the normal distribution of the quantitative variable and homogeneity of the variance, while comparison of frequencies was made by the chi-square test or by the Fisher's test when categories have expected frequencies less than 5 in more than 20% of cases.

Survival Analysis

Survival analysis was performed using the Kaplan–Meier method to compare the types of diagnosis. In addition, Cox regression analysis was applied to estimate the risk of death and adjusted with entry criteria for the following variables: age, comorbidity (presence, absence), and tumor stage (*in situ*, Stage I, Stage II, Stage III). The relative risk and the corresponding 95% confidence interval were calculated. In the survival study, the primary endpoint was time elapsed to death from breast cancer from the time of diagnosis. Survival times for patients who were still alive were assumed to be the last date of follow-up. Patients who were still alive at the closing date were censored.

Results

We segmented and compared patient data for interval and screening breast cancer (incident and prevalent). The univariate analysis showed significant differences, with screening cases presenting at a higher mean ± standard deviation age of 58.8±5.5 years than interval cases 57.7±5.3 years (p = 0.002), as well as with a higher frequency of hormone receptors expression (p<0.001) and luminal A and luminal B phenotypes (p = 0.001). Screening tumors also presented with a significantly different phenotype, with a lower frequency of triple negative tumors (p = 0.001), less advanced stage (p<0.001) and lower grade (p<0.001) and fewer deaths (p<0.001). We also found a tendency (p<0.1) for screening cases to have a family history of breast cancer more frequently than interval cases. We did not find any significant differences for comorbidity, Charlson Index, HER-2 enrichment or Ki-67 expression variables (Table 1).

The improved survival of screening cases is also evident in both the survival function (Figure 1) and the multivariate Cox regression analysis, in which interval cases [hazard ratio (HR): 1.63, confidence interval (CI) = 1.13–2.36; p = 0.01] as well as the presence of comorbidity (HR: 1.48, CI = 1.05–2.10; p = 0.03) and advanced stage (HR: 4.82, CI = 1.17–19.80 for stage I; HR: 4.96, CI = 1.19–20.62 for stage II and HR: 16.25, CI = 3.89–67.77 for stage III; p<0.001) were associated with an increased risk of death (Table 2).

We also found significant differences between prevalent and incident cases. In this situation, patients with prevalent tumors presented at a lower mean age (p<0.001), with a lower frequency of comorbidity (p = 0.038) and a tendency (p = 0.051) to be diagnosed as triple negative less frequently. We did not find significant differences for the rest of the variables studied (Table 3).

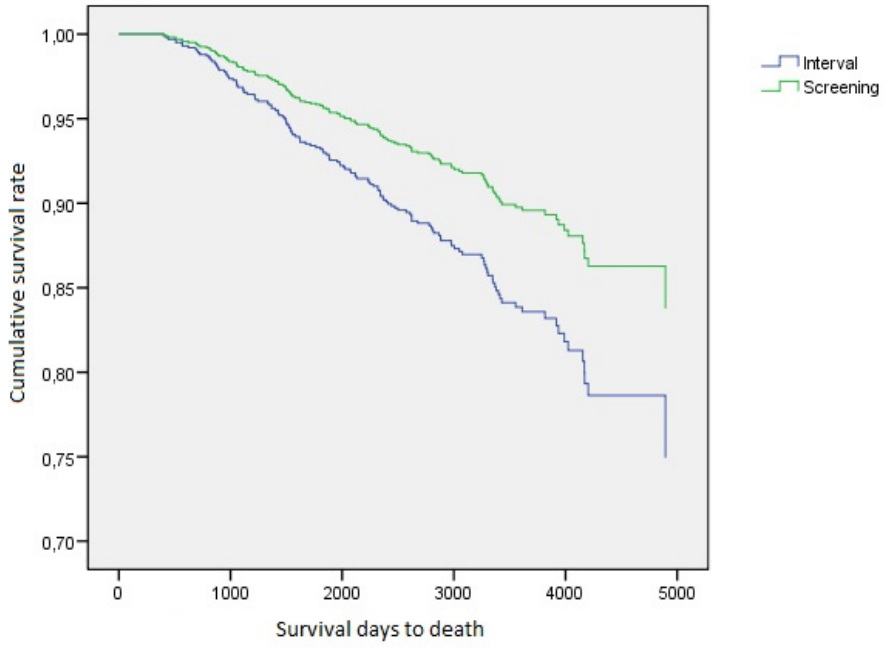

Figure 1. Overall survival curve (Kaplan–Meier) for interval and screening cases. Compared to interval cases, the Kaplan–Meier analysis shows improved survival of screening cases. Number of cases is 1,086, 158 deaths and 4,657 days as median follow-up time for both groups. Hazard ratio (HR): 2.53 [confidence interval (CI): 95%: 1.84-3.46] and p<0.001 from a univariate Cox model

Table 1. Sociodemographic and clinical characteristics of patients with interval and screening breast cancer

Variables	Interval (n = 345)		Screening (n = 741)		*p*-value
	n	%	n	%	
Age at diagnosis					
Mean ± SD	57.7	5.3	58.8	5.5	0.002**
Comorbidity					
Absence	254	73.6	534	72.1	0.643
Presence	91	26.4	207	27.9	
Charlson Index					
Mean ± SD	0.79	1.60	0.76	1.56	0.78
Family history[1]					
No	201	90.5	519	85.8	0.091
Yes	21	9.5	86	14.2	
Phenotype[2]					
Luminal A	140	45.9	278	56.9	0.001***
Luminal B	82	26.9	133	27.2	
HER-2	33	10.8	38	7.8	
TNBC	50	16.4	40	8.2	
Stage[3]					
In situ	14	4.2	88	12.2	<0.001***
I	88	26.6	385	53.3	
II	144	43.5	199	27.5	
III	85	25.7	51	7.1	
Estrogen receptors					
Negative	97	28.1	127	17.1	<0.001***
Positive	248	71.9	614	82.9	
Progesterone receptors[4]					
Negative	147	42.7	233	31.5	<0.001
Positive	197	57.3	507	68.5	
HER-2[5]					
Negative	242	77.6	401	79.9	0.484
Positive	70	22.4	101	20.1	
Ki-67 expression					
<14%	107	53.2	103	45	0.107
>14%	94	46.8	126	55	
Grade[7]					
I	51	17.9	183	31.1	<0.001***
II	107	37.5	252	42.9	
III	127	44.6	153	26	

Missing data: [1] = 259, [2] = 292, [3] = 32, [4] = 2, [5] = 272, [6] = 656, [7] = 213.
**Very significant; ***Highly significant
TNBC: triple negative breast cancer; HER-2: human epidermal growth factor receptor 2; SD: standard deviation; n: number

Table 2. Factors related to overall mortality by Cox regression analysis: screening and interval cases

Risk factor	*p*-value	HR	CI 95%	
			Lower	Upper
Type of diagnosis				
Screening	0.01	1.00		
Interval		1.63	1.13	2.36
Age	0.15	1.02	0.99	1.06
Comorbidity				
Absence	0.03	1.00		
Presence		1.48	1.05	2.10
Stage				
In situ	<0.001	1.00		
I		4.82	1.17	19.80
II		4.96	1.19	20.62
III		16.25	3.89	67.77

HR: hazard ratio; CI: confidence interval

The multivariate analysis showed an increased risk of death for advanced stages (HR: 3.88, CI = 0.94–16.10 for stage I; HR: 3.26, CI = 0.75–14.18 for stage II and HR: 15.69, CI = 3.62–68.12 for stage III; $p<0.001$) and also revealed a similar behavior in survival numbers for both cancer subgroups (Table 4).

Discussion and Conclusion

Our study of a large series of screening-detected breast carcinomas shows that not only variables which are generally associated with a less aggressive behavior and a better prognosis are more frequent in screening tumors than in interval tumors but also that, among screening tumors, prevalent cases exhibit the most favorable prognostic factors. Specifically, our study shows the existence of a number of biological and clinical-pathological features among screening-detected breast tumors subtypes which reinforce the idea that the method of detection should be considered in risk estimations and avoid the use of aggressive treatments in those cases with a more favorable prognosis, such as breast cancer patients with prevalent tumors.

Consistent with other published studies reporting that the risk of distant metastases can be overestimated for breast cancer patients diagnosed by mammography screening unless the method of detection (mammography screening or other methods) is taken into account in the risk estimation (11), our results show that the method of detection can be considered as a prognostic factor for breast cancer patients, even after adjusting for known tumor characteristics (12, 24, 25) possibly due to differences in tumor features and biology (13, 20, 26, 27). Specifically, we reveal that, compared to interval tumors, screening-detected breast tumors present with less aggressive biological characteristics and more favorable prognostic features, such as low-grade, early-stage, expression of hormone receptors and Luminal A or Luminal B phenotypes, improved survival, and lower mean age as well as a tendency to have a higher frequency of cancer family history. Our results are in keeping with previous studies from our research group (28). These observed that screening cases showed different biological characteristics that are generally associated with reduced tumor aggressiveness and enhanced survival, such as positive expression of hormone receptors**.** Accordingly, interval cases are characterized by more-aggressive tumor characteristics and poorer survival outcomes (18, 20, 29) than screening-detected cases, despite receiving more adjuvant chemotherapy (28, 30).

Altogether, our results would support the need for cancer trialists to routinely collect information about method of detection when determining risk estimations (12) and the potential utility of considering the time of diagnosis within a breast screening program during decision-making on the best treatment strategy for the patient.

We also studied if there were any clinical or prognostic differences between prevalent and incident screening groups. We observed that prevalent tumors were characterized by some features, such as lower mean patient age, lower frequency of comorbidity and have a tendency to be diagnosed as triple negative less frequently (Table 2), generally associated with a better prognosis. Although a previous study from our group in a different cohort also found an association with an improved survival for prevalent screen-detected breast tumors (21), we did not find this survival advantage over incident tumors in this series, which would justify further studies with additional patient cohorts. Despite these contradictory results, considering that the prognosis of prevalent cases would not be affected by the use of adjuvant chemotherapy (28), tumor trialists should routinely collect information about method of detection (12), since the inclusion of the type of screening-detected breast cancer subgroup in clinical practice guidelines could help provide patients with the best care options.

Table 3. Sociodemographic and clinical characteristics of patients with prevalent and incident breast cancer

Variables	Prevalent (n = 188)		Incident (n = 553)		*p*-value
	n	%	n	%	
Age					
Mean ± SD	54.3	4.9	60.3	4.8	<0.001***
Comorbidity					
Absence	147	78.2	387	70	0.038*
Presence	41	21.8	166	30	
Charlson Index					
Mean ± SD	0.62	1.46	0,81	1.59	0.161
Family history[1]					
No	132	87.4	387	85.2	0.597
Yes	19	12.6	67	14.8	
Phenotype[2]					
Luminal A	60	60.0	218	56.0	0.051
Luminal B	27	27.0	106	27.2	
HER-2	11	11.0	27	6.9	
TNBC	2	2.0	38	9.8	
Stage[3]					
In situ	26	14.4	62	11.4	0.725
I	92	50.8	293	54.1	
II	51	28.2	148	27.3	
III	12	6.6	39	7.2	
Estrogen receptors					
Negative	32	17.0	95	17.2	1
Positive	156	83.0	458	82.8	
Progesterone receptors[4]					
Negative	50	26.6	183	33.2	0.114
Positive	138	73.4	369	66.8	
HER-2[5]					
Negative	78	77.2	323	80.5	0.545
Positive	23	22.8	78	19.5	
Ki-67 expression					
<14%	28	48.3	75	43.9	0.666
>14%	30	51.7	96	56.1	
Grade[7]					
I	48	34.8	135	30.0	0.199
II	62	44.9	190	42.2	
III	28	20.3	125	27.8	

*Significant; ***Highly significant

Missing data: [1] = 259; [2] = 292; [3] = 32; [4] = 2; [5] = 272; [6] = 656; [7] = 213

TNBC: triple negative breast cancer; HER-2: human epidermal growth factor receptor 2; SD: standard deviation; n: number

Table 4. Factors related to overall mortality by Cox regression analysis: prevalent and incident cases

Risk factor	β	p-value	HR	CI 95%	
				Lower	Upper
Type of diagnosis					
Prevalent			1.00		
Incident	0.01	0.98	1.01	0.56	1.81
Age	0.04	0.10	1.04	0.99	1.09
Comorbidity					
Absence			1.00		
Presence	0.18	0.46	1.20	0.73	1.97
Stage					
In situ			1.00		
I	1.36		3.88	0.94	16.10
II	1.18	<0.001	3.26	0.75	14.18
III	2.75		15.69	3.62	68.12

HR: hazard ratio; CI: confidence interval

In conclusion, our results show that risk factors may be overestimated for breast cancer patients diagnosed by screening programs when the method of detection is not considered. Furthermore, our results suggest a need to continue investigating patient survival and clinical-pathological differences between breast tumors detected by screening, highlighting the potential benefit that patient risk stratification according to the screening subgroup to which they belong (prevalent, interval, incident) can have to optimize their clinical management and treatment.

Acknowledgments

The authors are grateful to María del Carmen Delgado Navarro for her excellent technical assistance.

Ethics Committee Approval: This study was approved by Costa del Sol Hospital Ethics Committee (decision/file number: 003-Nov-PR2, date: 24.11.2016).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions

Concept: M.G., X.C., M.S., M.R.; Methodology: I.Z., T.T., D.P., F.M.C., K.M., L.D., M.M.V., M.P.R.; Analysis and/or Interpretation: J.L., F.R.R.; Writing: M.G., M.R., M.S.; Funding acquisition: M.R.; Supervision: M.R

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: This research was partially supported by grants from REDISSEC (RD12/0001/0010 and RD16/0001/0006), RICAPPS (RD21/0016/0015), Consejería de Salud Junta de Andalucia (PI 16/0298) and the European Regional Development Fund. The researcher Marilina García-Aranda is the benefactor of a postdoctoral contract financed by the European Social Fund - Operational Program of Andalusia 2014-2020 for the "Incorporation of Research Personnel with a PhD degree in the field of Health Sciences and Technologies in R&D and Innovation Centers of the Public Health System of Andalusia" (RH-0055-2020).

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2020; 70: 313. (PMID: 32767693) [Crossref]
2. Moller H, Davies E. Over-diagnosis in breast cancer screening. BMJ 2006; 332: 691-692. (PMID: 16517549) [Crossref]
3. Shah TA, Guraya SS. Breast cancer screening programs: Review of merits, demerits, and recent recommendations practiced across the world. J Microsc Ultrastruct 2017; 5: 59-69. (PMID: 30023238) [Crossref]
4. Day NE. Overdiagnosis and breast cancer screening. Breast Cancer Res 2005; 7: 228-229. (PMID: 16168144) [Crossref]
5. Broeders M, Moss S, Nyström L, Njor S, Jonsson H, Paap E, et al. The impact of mammographic screening on breast cancer mortality in Europe: a review of observational studies. J Med Screen 2012; 19(Suppl 1): 14-25. (PMID: 22972807) [Crossref]
6. Duggan C, Trapani D, Ilbawi AM, Fidarova E, Laversanne M, Curigliano G, et al. National health system characteristics, breast cancer stage at diagnosis, and breast cancer mortality: a population-based analysis. Lancet Oncol 2021; 22: 1632-1642 (PMID: 34653370) [Crossref]
7. Lyratzopoulos G, Abel G. Earlier diagnosis of breast cancer: focusing on symptomatic women. Nat Rev Clin Oncol 2013: 10. (PMID: 23881030)
8. Donzelli A. The benefits and harms of breast cancer screening. Lancet 2013; 381: 799-800. (PMID: 23668504) [Crossref]
9. Dillon MF, Hill AD, Quinn CM, O'Doherty A, Crown J, Fleming FJ, et al. Surgical intervention in screen-detected patients versus symptomatic patients with breast cancer. J Med Screen 2004; 11: 130-134. (PMID: 15333271) [Crossref]

10. Welch HG, Black WC. Using autopsy series to estimate the disease "reservoir" for ductal carcinoma in situ of the breast: how much more breast cancer can we find? Ann Intern Med 1997; 127: 1023-1028. (PMID: 9412284) [Crossref]
11. Joensuu H, Lehtimäki T, Holli K, Elomaa L, Turpeenniemi-Hujanen T, Kataja V, et al. Risk for distant recurrence of breast cancer detected by mammography screening or other methods. JAMA 2004; 292: 1064-1073. (PMID: 15339900) [Crossref]
12. Shen Y, Yang Y, Inoue LY, Munsell MF, Miller AB, Berry DA. Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. J Natl Cancer Inst 2005; 97: 1195-1203. (PMID: 16106024) [Crossref]
13. Wishart GC, Greenberg DC, Britton PD, Chou P, Brown CH, Purushotham AD, et al. Screen-detected vs symptomatic breast cancer: is improved survival due to stage migration alone? Br J Cancer 2008; 98: 1741-1744. (PMID: 18506175) [Crossref]
14. Dawson SJ, Duffy SW, Blows FM, Driver KE, Provenzano E, LeQuesne J, et al. Molecular characteristics of screen-detected vs symptomatic breast cancers and their impact on survival. Br J Cancer. 2009;101(8):1338-1344. (PMID: 19773756) [Crossref]
15. Collett K, Stefansson IM, Eide J, Braaten A, Wang H, Eide GE, et al. A basal epithelial phenotype is more frequent in interval breast cancers compared with screen detected tumors. Cancer Epidemiol Biomarkers Prev 2005; 14: 1108-1112. (PMID: 15894660) [Crossref]
16. Musolino A, Michiara M, Conti GM, Boggiani D, Zatelli M, Palleschi D, et al. Human epidermal growth factor receptor 2 status and interval breast cancer in a population-based cancer registry study. J Clin Oncol 2012; 30: 2362-2368. (PMID: 22585698) [Crossref]
17. Houssami N, Hunter K. The epidemiology, radiology and biological characteristics of interval breast cancers in population mammography screening. NPJ Breast Cancer 2017; 3: 12. (PMID: 28649652) [Crossref]
18. Grassmann F, He W, Eriksson M, Gabrielson M, Hall P, Czene K. Interval breast cancer is associated with other types of tumors. Nat Commun 2019; 10: 4648. (PMID: 31641120) [Crossref]
19. Domingo L, Salas D, Zubizarreta R, Baré M, Sarriugarte G, Barata T, et al. Tumor phenotype and breast density in distinct categories of interval cancer: results of population-based mammography screening in Spain. Breast Cancer Res 2014; 16: R3. (PMID: 24410848) [Crossref]
20. Irvin VL, Zhang Z, Simon MS, Chlebowski RT, Luoh SW, Shadyab AH, et al. Comparison of Mortality Among Participants of Women's Health Initiative Trials With Screening-Detected Breast Cancers vs Interval Breast Cancers. JAMA Netw Open 2020; 3: e207227. (PMID: 32602908) [Crossref]
21. Redondo M, Funez R, Medina-Cano F, Rodrigo I, Acebal M, Tellez T, et al. Detection methods predict differences in biology and survival in breast cancer patients. BMC Cancer 2012; 12: 604. (PMID: 23244222) [Crossref]
22. Ascunce N, Salas D, Zubizarreta R, Almazán R, Ibáñez J, Ederra M, et al. Cancer screening in Spain. Ann Oncol 2010; 21(Suppl 3): iii43-51. (PMID: 20427360) [Crossref]
23. García-Gutierrez S, Orive M, Sarasqueta C, Legarreta MJ, Gonzalez N, Redondo M, et al. Health services research in patients with breast cancer (CAMISS-prospective): study protocol for an observational prospective study. BMC Cancer 2018; 18: 54. (PMID: 29310641) [Crossref]
24. Puvanesarajah S, Gapstur SM, Patel AV, Sherman ME, Flanders WD, Gansler T, et al. Mode of detection and breast cancer mortality by follow-up time and tumor characteristics among screened women in Cancer Prevention Study-II. Breast Cancer Res Treat 2019; 177: 679-689. (PMID: 31264062) [Crossref]
25. Shen SC, Ueng SH, Yang CK, Yu CC, Lo YF, Chang HK, et al. Impact of Detection Method and Accompanying Ductal Carcinoma in Situ on Prognosis of T1a, bN0 Breast Cancer. J Cancer 2017; 8: 2328-2335. (PMID: 28819437) [Crossref]
26. Caldarella A, Puliti D, Crocetti E, Bianchi S, Vezzosi V, Apicella P, et al. Biological characteristics of interval cancers: a role for biomarkers in the breast cancer screening. J Cancer Res Clin Oncol 2013; 139: 181-185. (PMID: 22961208) [Crossref]
27. Kirsh VA, Chiarelli AM, Edwards SA, O'Malley FP, Shumak RS, Yaffe MJ, et al. Tumor characteristics associated with mammographic detection of breast cancer in the Ontario breast screening program. J Natl Cancer Inst 2011; 103: 942-950. (PMID: 21540443) [Crossref]
28. Zarcos-Pedrinaci I, Redondo M, Louro J, Rivas-Ruiz F, Téllez T, Pérez D, et al. Impact of adjuvant chemotherapy on the survival of patients with breast cancer diagnosed by screening. Cancer Med 2019; 8: 6662-6670. (PMID: 31549794) [Crossref]
29. Bellio G, Marion R, Giudici F, Kus S, Tonutti M, Zanconati F, et al. Interval breast cancer versus screen-detected cancer: comparison of clinicopathologic characteristics in a single-center analysis. Clin Breast Cancer 2017; 17: 564-571. (PMID: 28456487) [Crossref]
30. Rayson D, Payne JI, Abdolell M, Barnes PJ, MacIntosh RF, Foley T, et al. Comparison of clinical-pathologic characteristics and outcomes of true interval and screen-detected invasive breast cancer among participants of a Canadian breast screening program: a nested case-control study. Clin Breast Cancer 2011; 11: 27-32. (PMID: 21421519) [Crossref]

Case Report

Eur J Breast Health 2022; 18(2): 190-194
DOI: 10.4274/ejbh.galenos.2021.6278

Breast Hemangioma Evaluation with Magnetic Resonance Imaging: A Rare Case Report

Özge Aslan[1], Ayşenur Oktay[1], Gürdeniz Serin[2], Levent Yeniay[3], Orkhan Aghamirzayev[1]

[1]Department of Radiology, Ege University Faculty of Medicine, İzmir, Turkey
[2]Department of Medical Pathology, Ege University Faculty of Medicine, İzmir, Turkey
[3]Department of General Surgery, Ege University Faculty of Medicine, İzmir, Turkey

ABSTRACT

Vascular tumors are rare in the breasts, and the most common forms include hemangiomas and angiosarcomas. Hemangiomas are rare benign vascular tumors. Most of them are asymptomatic and nonpalpable clinically, and the vast majority of such lesions are detected incidentally by mammography. Breast hemangiomas are difficult to diagnose using conventional imaging modalities since their imaging findings are variable. The following is a case presentation of an asymptomatic forty-five-year old female patient who was diagnosed with a rare hemangioma. Physical examination, ultrasonography (US) and mammographic examination were normal. Dynamic contrast enhanced magnetic resonance imaging (MRI) showed a non-mass pathological enhancement. After a short-term follow up, a comparative MRI was obtained and biopsy was planned, due to the heterogeneous non-mass enhancement on MRI. Needle core biopsy with US guidance was performed, resulting in benign findings. However, because of the discordance between imaging and histopathology, an MRI-guided wire localization followed by open surgical biopsy was performed. Histopathologic evaluation reported capillary hemangioma.The imaging findings, including US, mammography and MRI, of hemangioma are reviewed and described in this case report.

Keywords: Breast; hemangioma; angiosarcoma; MRI

Cite this article as: Aslan Ö, Oktay A, Serin G, Yeniay L, Aghamirzayev O. Breast Hemangioma Evaluation with Magnetic Resonance Imaging: A Rare Case Report. Eur J Breast Health 2022; 18(2): 190-194

Key Points

- Benign hemangiomas can occur in the breast parenchyma and are usually small and incidentally found on excisional biopsy for other lesions.
- Hemangiomas are rare benign vascular tumors.
- Differential diagnosis of any type of hemangioma within the breast should be well-differentiated angiosarcoma.
- Due to the potential malignancy risk in vascular breast tumors, surgical excision is recommended in all cases of breast hemangioma.

Introduction

Vascular tumors are rare in the breasts, and the most common forms include angiosarcomas and hemangiomas. Hemangiomas are usually seen in adult women at any age (19 to 82 years with a mean of 60 years) (1). Hemangiomas are usually found incidentally through imaging techniques, including mammography, ultrasonography (US) or magnetic resonance imaging (MRI) (2).

In this case, the breast hemangioma was not visible on US or mammography and could not be differentiated from malignancy with MRI, eventually requiring open biopsy.

Case Presentation

A 45-year-old female patient was referred to our clinic for evaluation of MRI taken at another hospital. There was a weak heterogeneous nonmass contrast enhancement in the upper inner quadrant of the right breast on dynamic, contrast-enhanced MRI (Figures 1 and 2).

She had no previous history of breast-related problems, radiation treatment, or family history of breast or ovarian cancer. The only complaint was breast pain, and there was no skin color change and no finding on physical examination of the breasts. Mammography and ultrasonography were performed at our clinic. There was a mass opacity in the upper outer quadrant on the mammograms, which was confirmed as a cyst on US.

Corresponding Author:
Özge Aslan; dr.ozgeaslan@gmail.com

Received: 20.10.2020
Accepted: 30.01.2021
Available Online Date: 01.04.2022

No suspicious finding was present in the inner upper quadrant either with mammography and US (Figure 3).

A follow-up appointment was scheduled for three months later. Craniocaudal (CC) view mammogram and US of the right breast were negative. Therefore, follow-up MRI was performed using a 3-T MR imaging unit (Siemens MAGNETOM® Verio) with the patient prone and breast positioned within a dedicated surface breast coil with seven-channels. The MRI images were acquired using the following sequences: axial, fat-suppressed, and fast spin-echo T2-weighted imaging sequence and pre-contrast and post-contrast dynamic axial T1-weighted three-dimensional, fat-suppressed, fat-spoiled, gradientecho sequence.

The images were obtained before and after a rapid bolus injection of gadolinium- diethylenetriamine penta acetic acid (Magnevist; Schering, Berlin, Germany) at 0.1 mmol/kg of body weight.

In the early phase of dynamic contrast MRI, a non-mass heterogeneous pathologic enhancement, 4 cm in size, was seen in this area. The enhancement was continued and the finding was more evident from the previous MRI in the delayed phase with type 2 kinetic curve (Figure 4). It was categorized as Breast Imaging Reporting and Data System (BI-RADS) 4.

An US-guided core biopsy was performed, using the coordinates of the lesion obtained with MRI, which resulted in benign histopathological findings of fibrocystic changes of the breast and sclerosing adenosis.

Due to the discordance between radiology and pathology results, we recommended a second biopsy with MRI guidance. The patient requested surgical examination and so we performed an MRI-guided hook wire localization followed by open biopsy (Figure 5a). Once the lesion was localized, the MRI-compatible guide hook wire was introduced to the appropriate depth. After the appropriate location and depth was confirmed, a guide wire was deployed through the needle.

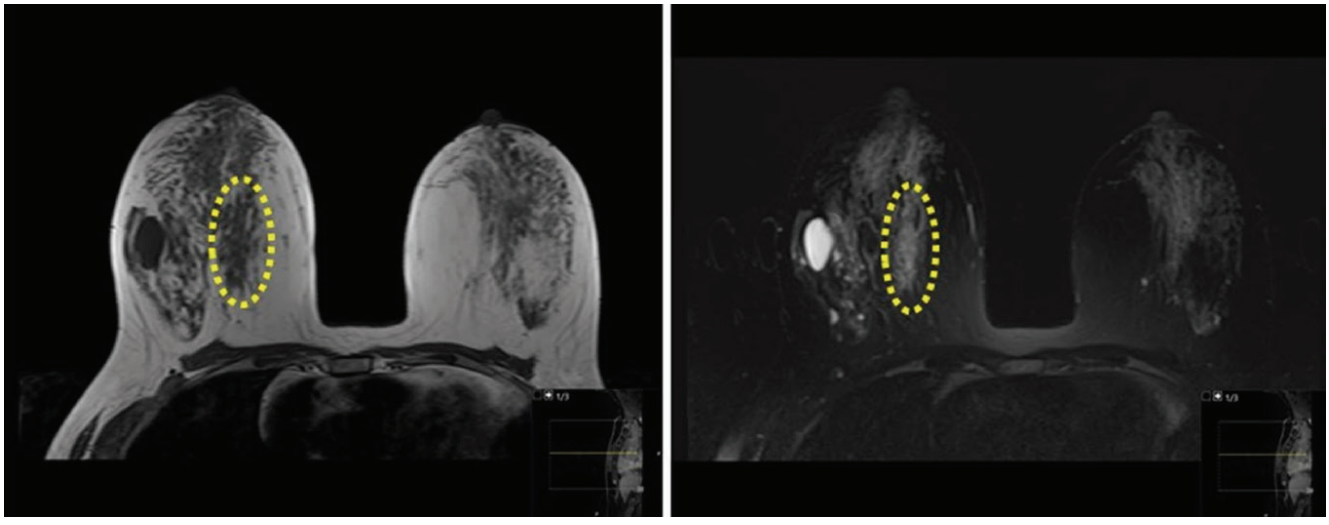

Figure 1. T1W and T2W MRI ; the circle indicates asymmetric tissue in the upper inner quadrant of the right breast that was isointense with breast tissue on T1W MRI and slightly hyperintense on T2W MR image

MRI: magnetic resonance imaging

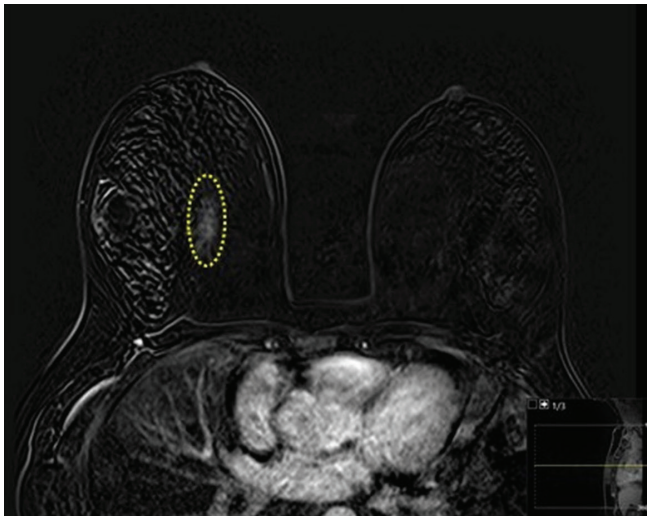

Figure 2. Dynamic, contrast-enhanced MRI subtracted image showing a weak non-mass enhancement in the upper inner quadrant of right breast

MRI: magnetic resonance imaging

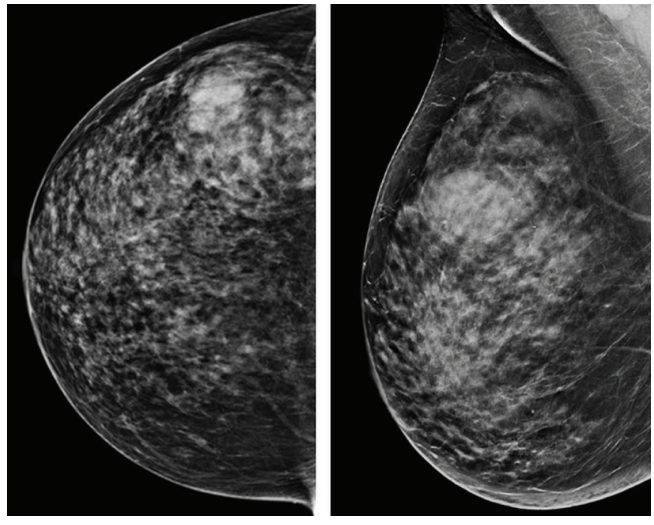

Figure 3. On US, there was a mass opacity of a cyst in the upper outer quadrant of the right breast; there were no suspicious findings in the inner quadrant on mammography images

US: ultrasonography

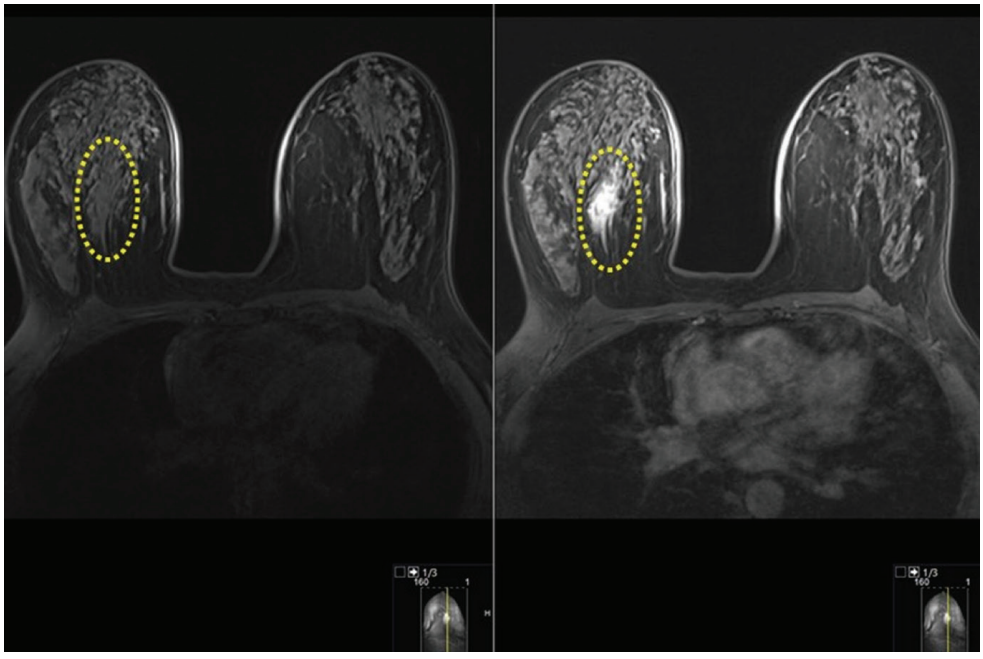

Figure 4. On pre-contrast T1W MRI, there was a 4 cm hypointense asymmetric lesion with irregular borders in the upper inner quadrant of the right breast. On postcontrast T1W image non-mass enhancement was seen which became more evident at a subsequent follow-up three months later

MRI: magnetic resonance imaging

After MRI, a mammogram was taken in the CC position in order to understand the location and depth of the wire and to show its interference with the surrounding tissue and nipple. After the excision, a specimen mammography was taken (Figure 5b).

On macroscopic evaluation of excision material, there was an irregularly circumscribed lesion (Figure 6). Histopathological evaluation revealed numerous vascular spaces, randomly distributed within the breast tissue, with no sign of anastomosis (Figures 7a and 7b).

Immunohistochemical study showed positive staining for endothelial markers such as CD31 and ERG in vascular spaces scattered between normal breast ducts (Figure 8). Final histopathological diagnosis of the lesion was capillary hemangioma.

Discussion and Conclusion

Benign vascular breast lesions, including hemangioma and angiomatosis, are rare (1). Angiosarcoma, which is one of the malignant vascular tumors and is usually a very aggressive tumor, is less common than the benign vascular tumors (1). In the literature, there is no evidence that benign vascular tumors, with or without atypia, are later upgraded to angiosarcoma (3, 4). However, when hemangioma is detected by needle biopsy, surgical excision is preferred because the sample taken may coincide with the well-differentiated area of a possible underlying angiosarcoma (1). Thus, it is clearly very important to be able to make the differential diagnosis of hemangioma and angiosarcoma.

Breast hemangiomas have variable imaging features (5). Benign hemangiomas can occur in the breast parenchyma and are usually small and incidentally found on excisional biopsy for other lesions (4, 6). Most common types are capillary and cavernous hemangioma (7).

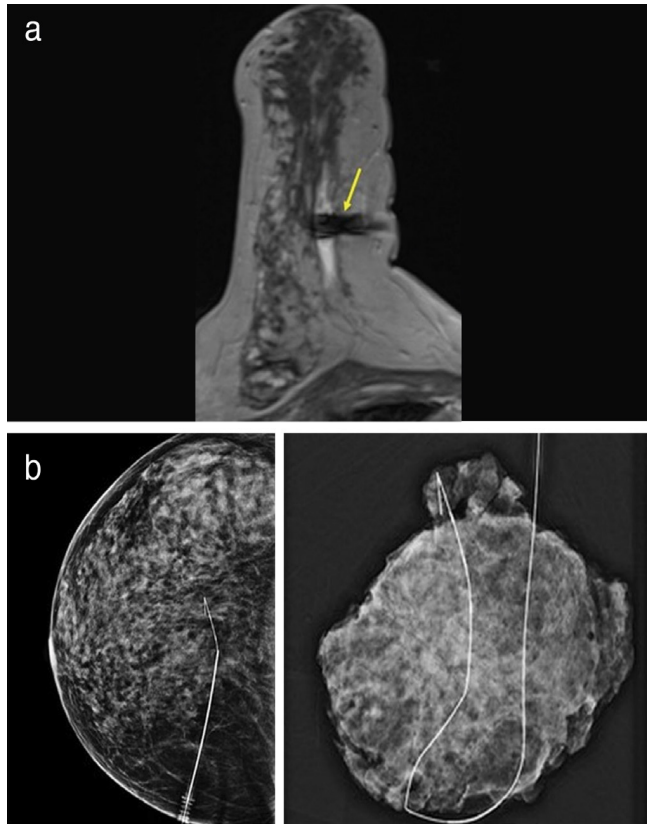

Figure 5. a) Susceptibility artefact of the hook wire is seen in the lesion on axial dynamic contrast enhanced T1W images. **b)** Mammography shows location of the hook wire system and specimen mammography shows the excised area with the wire

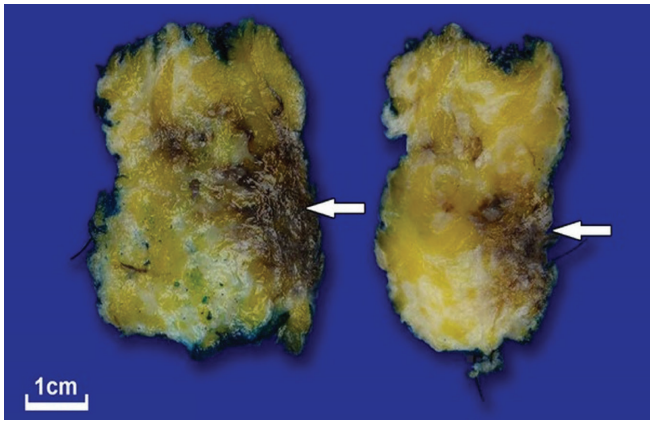

Figure 6. Macroscopic view of an irregularly demarcated lesion, 4.0 x 1.8 cm, with a hemorrhagic cross-sectional surface, abutting the margin of the surgical excision, in serial sections of partial mastectomy material

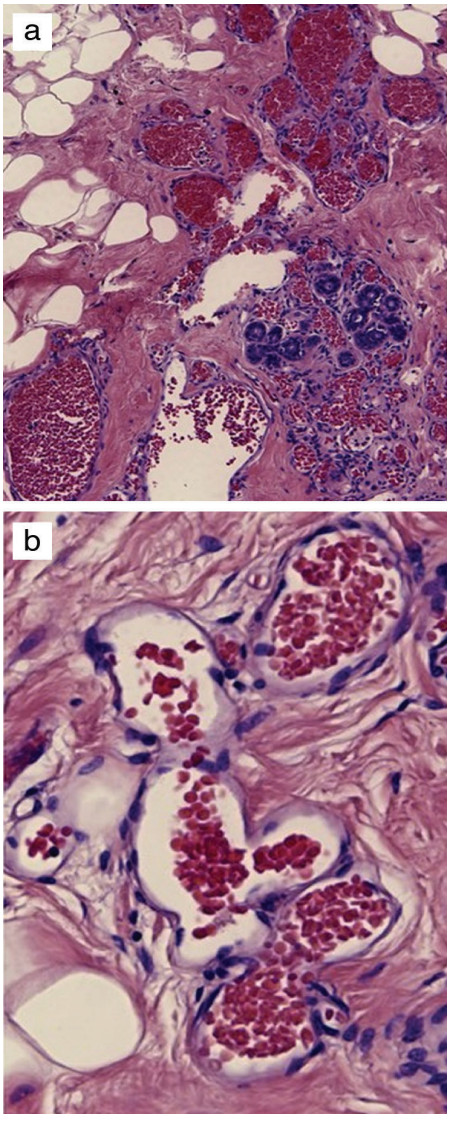

Figure 7. a) Vascular spaces scattered around the breast ducts, without significant anastomosis, containing erythrocytes (hematoxylin & eosin, 200x). **b)** Vascular spaces lined with a single layer of endothelium without signs of proliferation or atypia (hematoxylin & eosin, 400x).

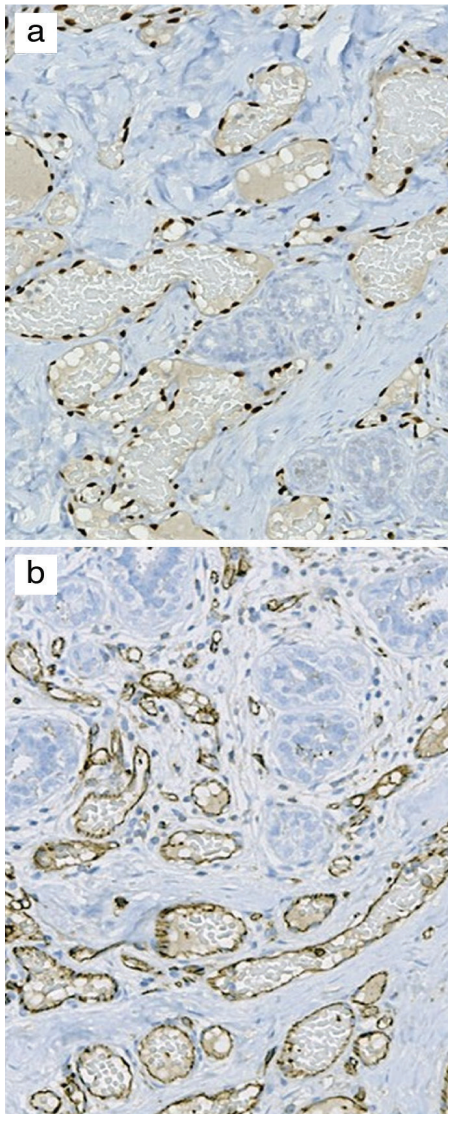

Figure 8. Positive staining for endothelial markers in vascular spaces scattered between and around normal breast ducts, in immunohistochemical study. **a)** ERG nuclear positivity, 200x, **b)** CD31, cytoplasmic positivity, 200x)

ERG: erythroblast transformation-specific related gene

Breast hemangiomas may have nonspecific features on mammograms and usually there is no finding in these patients. Some hemangiomas may show a mass opacity with well-defined margins, with or without calcifications (8). On US examination, a hemangioma might be seen as an oval solid mass with circumscribed or microlobulated margins, and the echotexture can be hypoechoic, isoechoic or heterogeneous (8).

MRI demonstrates a variable appearance, depending on the size and subtype of the hemangioma. Hemangiomas are isointense with muscle in T1W images and hyperintense in T2W images. Also, there may be hypointense areas in the lesion because of calcifications, phleboliths and fibrous tissue in T2W images. These features are important for differentiation with malignancy. Dynamic, contrast-enhanced MRI is necessary for accurate determination of the size and distribution of the lesion. Hemangiomas have an early and diffuse enhancement pattern in dynamic, contrast-enhanced MRI.

The differential diagnosis must be made between any type of hemangioma within the breast and the possibility of a well-differentiated angiosarcoma, because in the latter, prognosis is poor. Angiosarcoma is of two types, primary and secondary (9, 10). In angiosarcoma, US and mammography may sometimes seem completely normal (11). As in our case, US and mammography findings may not be present, and hemangioma and angiosarcoma cannot be differentiated without tissue biopsy. In some cases, especially when the lesion is small, US and mammography cannot identify the lesion. MRI is a more sensitive modality than US and mammography. Hemangiomas enhance in the early phase of dynamic, contrast-enhanced MRI. Surgical excision is recommended because of this feature and because of the malignant potential of a hemangioma (12, 13). In our case, the MRI enhancement pattern mimicked malignancy and the lesion was only evident in MRI. The discordance between radiological and pathological findings prompted open surgical biopsy after needle wire localization with MRI guidance.

In conclusion, in the breast, hemangioma imaging findings can mimic malignancy. As there is a potential malignancy risk in vascular breast tumors, surgical excision and imaging follow-up is recommended in all cases of breast hemangioma.

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.A., A.O., L.Y.; Concept: Ö.A., A.O.; Design: Ö.A., A.O. Data Collection and/or Processing: Ö.A., O.A., G.S., L.Y.; Analysis and/or Interpretation: Ö.A, A.O., O.A.; Literature Searching: Ö.A., A.O.; Writing: Ö.A., A.O., G.S.

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

Financial Disclosure: The authors declare that this study received no financial disclosure.

References

1. Lesueur GC, Brown RW, Bhathal PS. Incidence of perilobular hemangioma in the female breast. Arch Pathol Lab Med 1983; 107: 308-310. (PMID: 6687795) [Crossref]
2. Sebastiano C, Gennaro L, Brogi E, Morris E, Bowser ZL, Antonescu CR, et al. Benign vascular lesions of the breast diagnosed by core needle biopsy do not require excision. Histopathology 2017; 71: 795-804. (PMID: 28644513) [Crossref]
3. Hoda SA, Cranor ML, Rosen PP. Hemangiomas of the breast with atypical histological features. Further analysis of histological subtypes confirming their benign character. Am J Surg Pathol 1992; 16: 553-560. (PMID: 1599035) [Crossref]
4. Mesurolle B, Sygal V, Lalonde L, Lisbona A, Dufresne MP, Gagnon JH, et al. Sonographic and mammographic appearances of breast hemangioma. AJR Am J Roentgenol 2008; 191: W17-W22. doi: 10.2214/AJR.07.3153. (PMID: 18562711)[Crossref]
5. Kim SM, Kim HH, Shin HJ, Gong G, Ahn SH. Cavernous haemangioma of the breast. Br J Radiol 2006; 79: e177-e180. doi: 10.1259/bjr/11217388. (PMID: 17065282) [Crossref]
6. Apple SK, Dascalos JM, Bassett LW. Solid benign lesions of the breast. Bassett LW, Mahoney MC, Apple SK, D'Orsi CJ, editors. Breast Imaging. 1st ed. Philadelphia: Elsevier Saunders; 2011. p. 265-268. [Crossref]
7. Mango VL, Goodman S, Clarkin K, Wynn RT, Friedlander L, Hibshoosh H, et al. The unusual suspects: A review of unusual benign and malignant male breast imaging cases. Clin Imaging 2018; 50: 78-85. (PMID: 29328960) [Crossref]
8. Zafrakas M, Papasozomenou P, Eskitzis P, Zouzoulas D, Boulogianni G, Zaramboukas T. Cavernous breast hemangioma mimicking an ınvasive lesion on contrast Enhanced MRI. Case Rep Surg 2019; 2019: 2327892. (PMID: 31093413) [Crossref]
9. Monroe AT, Feigenberg SJ, Price Mendenhall N. Angiosarcoma after breast-conserving therapy. Cancer 2003; 97: 1832-1840. (PMID: 12673708) [Crossref]
10. Shet T, Malaviya A, Nadkarni M, Kakade A, Parmar V, Badwe R, et al. Primary angiosarcoma of the breast: observations in Asian Indian women. J Surg Oncol 2006; 94: 368-374. (PMID: 16967461) [Crossref]
11. Liberman L, Dershaw DD, Kaufman RJ, Rosen PP. Angiosarcoma of the breast. Radiology 1992; 183: 649-654. (PMID: 1584913) [Crossref]
12. Ameen R, Mandalia U, Marr A, Mckensie P. Breast Hemangioma: MR Appearance with Histopathological Correlation J Clin Imaging Sci 2012; 2: 53. (PMID: 23029636) [Crossref]
13. Funamizu N, Tabei I, Sekine C, Fuke A, Yabe M, Takeyama H, Okamoto T. Breast hemangioma with difficulty in preoperative diagnosis: a case report World J Surg Oncol 2014; 12: 313. (PMID: 25312096) [Crossref]

Case Report

Eur J Breast Health 2022; 18(2): 195-198
DOI: 10.4274/ejbh.galenos.2021.2021-10-5

A Rare Case of Granulomatous Mastitis in the Accessory Axillary Breast of a Pregnant Woman Successfully Treated by Surgery

Jun Nakamura, Futoshi Tanaka, Kazuma Ohtaka, Ken Sato, Akihiro Iyama

Department of Surgery, Yuai-Kai Foundation & Oda Hospital, Kashima, Japan

ABSTRACT

Granulomatous mastitis (GM) is a chronic inflammatory disease of the breast that usually occurs in women of reproductive age. However, GM during pregnancy is unusual and only one case of GM in the accessory breast has been reported so far. Here, we report an extremely rare case of GM in the accessory axillary breast of a pregnant woman. A 24-year-old pregnant woman had persistent pain and swelling in the right axilla that did not improve with antibiotic administration. Despite incision and drainage for subcutaneous abscess, the incised skin gradually became ulcerated, exposing the subcutaneous granulomatous tissue. *Corynebacterium* species were isolated in the bacterial culture of drained pus. Lower back pain, pain in several joints, and erythema nodosum on the lower legs appeared later. Based on the result of bacterial culture and the above disease course, the patient was clinically suspected of having GM. The axillary mass was surgically removed after childbirth, and the excised mass was histopathologically confirmed as GM. Treatment for GM should be considered individually and carefully in accordance with the patients' condition. Unnecessary surgery should be avoided. However, early addition of surgical interventions may yield good outcomes, especially for pregnant women because of limited treatment options.

Keywords: Axilla; granulomatous mastitis; pregnancy; surgery

Cite this article as: Nakamura J, Tanaka F, Ohtaka K, Sato K, Iyama A. A Rare Case of Granulomatous Mastitis in the Accessory Axillary Breast of a Pregnant Woman Successfully Treated by Surgery. Eur J Breast Health 2022; 18(2): 195-198

Key Points

- Granulomatous mastitis (GM) usually occurs in women of reproductive age, and only one case involved the accessory breast has been reported.
- No standard management for GM has been established, so treatment strategy should be planned individually.
- In the present case, surgery provided an early recovery from GM in the axilla during pregnancy.

Introduction

Granulomatous mastitis (GM) is an uncommon chronic inflammatory disease of the breast that presents with symptoms such as breast mass, abscess, erythema, induration, and tenderness. Although the etiology underlying GM remains unclear, a localized autoimmune inflammatory response to milk in the duct has been implicated in its pathogenesis. Thus, a correlation with breastfeeding and childbirth has been investigated (1). Previous reports have also associated GM with other clinical manifestations, such as erythema nodosum and, occasionally, with arthritis, suggesting that GM has an autoimmune component (2). Paviour et al. (3) was the first group to isolate *Corynebacterium* species in nine of 12 cases of GM. *Corynebacterium* is a lipophilic, Gram-positive, rod-shaped bacterium. Due to the lipophilicity, *Corynebacterium* infection has recently been suggested to be associated with the development of GM in lipid-rich mammary glands (3). Therapeutic strategies for GM include simple observation, antibiotic administration, steroid administration, drainage, excision, mastectomy, and combinations thereof. Here, we report a case of GM in the accessory axillary breast of a pregnant woman successfully treated by surgery.

Case Presentation

A 24-year-old pregnant woman visited an obstetrics clinic at 28 weeks 3 days of gestation with complaints of pain and swelling in the right axilla that had persisted for one week. Although intravenous piperacillin was given for three days, the symptoms worsened. Therefore, the patient was referred to our hospital. A fist-sized mass with redness and heat was noted in the right axilla (Figure 1). Ultrasonography revealed subcutaneous

Corresponding Author:
Jun Nakamura; jun19760712@hotmail.com

Received: 21.10.2021
Accepted: 30.11.2021
Available Online Date: 01.04.2022

abscess formation, so incision and drainage were performed on suspicion of pyogenic mastitis. However, the incised skin gradually became ulcerated, and the granulomatous tissue was exposed (Figure 2). *Corynebacterium* species were later isolated in the bacterial culture of drained pus. Pain in the lower back, elbows, hands, and ankles appeared at 30 weeks 5 days of gestation, and erythema nodosum appeared on the lower legs at 31 weeks 3 days of gestation. Based on the result of bacterial culture and the natural history of the condition, the patient was clinically suspected of having GM. A needle biopsy was considered to achieve definitive diagnosis, followed by systemic steroid therapy. However, the patient opted for elective surgery after childbirth, because she was about to give birth and had already endured a long period of suffering. Although two weeks of hospitalization was required from 34 weeks 3 days of gestation because of imminent premature birth, the patient gave birth at 36 weeks 3 days of gestation. The axial mass was surgically removed one week after delivery (Figure 3), and the excised mass was histopathologically confirmed as GM (Figure 4).

Discussion and Conclusion

Accessory breast tissue is subject to the same diseases as normally located breast tissue. The most frequent diseases reported in the accessory breasts are cancers, followed by mastitis, fibroadenoma, phyllodes tumor, and fibrocystic change (4). Yılmaz et al. (5) have recently reported a case of GM involving the accessory axillary breast. However, to our knowledge, there have been no other reports of GM in accessory breast tissue. GM usually occurs in women of reproductive age, and most cases occur around two years after breastfeeding, while GM during pregnancy is unusual (1). Moreover, GM is known to cause systemic inflammatory reactions, such as erythema nodosum and arthritis, as seen in our patient (1). It has been shown that rheumatologic conditions were present in 34% of published cases and erythema nodosum in 8% (6).

Although a standard therapeutic strategy has not yet been established, steroids are often administered for GM (6). Steroid therapy for GM was first described by DeHertogh et al. (7) in 1980, who recommended 30 mg/day prednisone for at least two months. Nevertheless, no

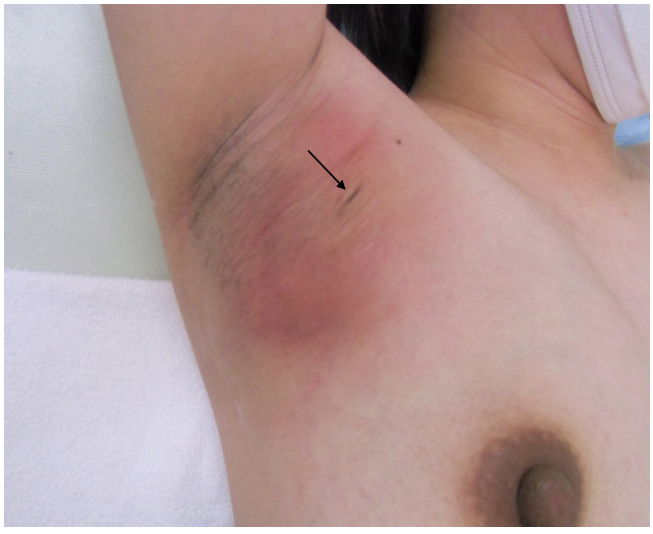

Figure 1. An image of the patient at the first visit

Arrow: accessory nipple

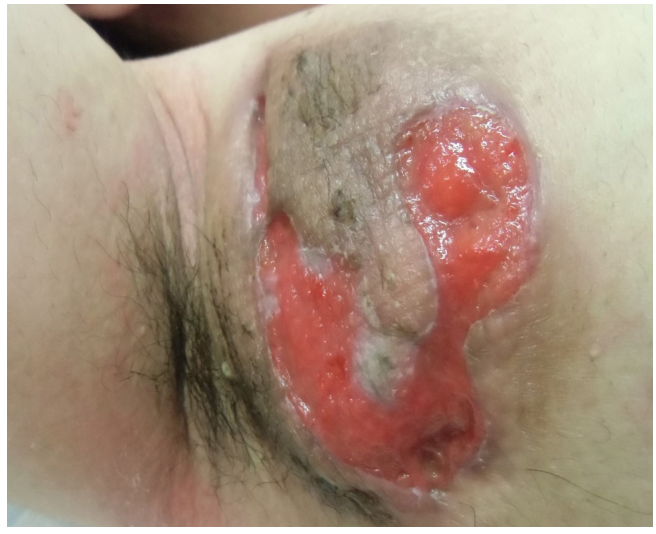

Figure 2. An image of the patient at 36 weeks 3 days of gestation. Incised skin was ulcerated and the granulomatous tissue was exposed

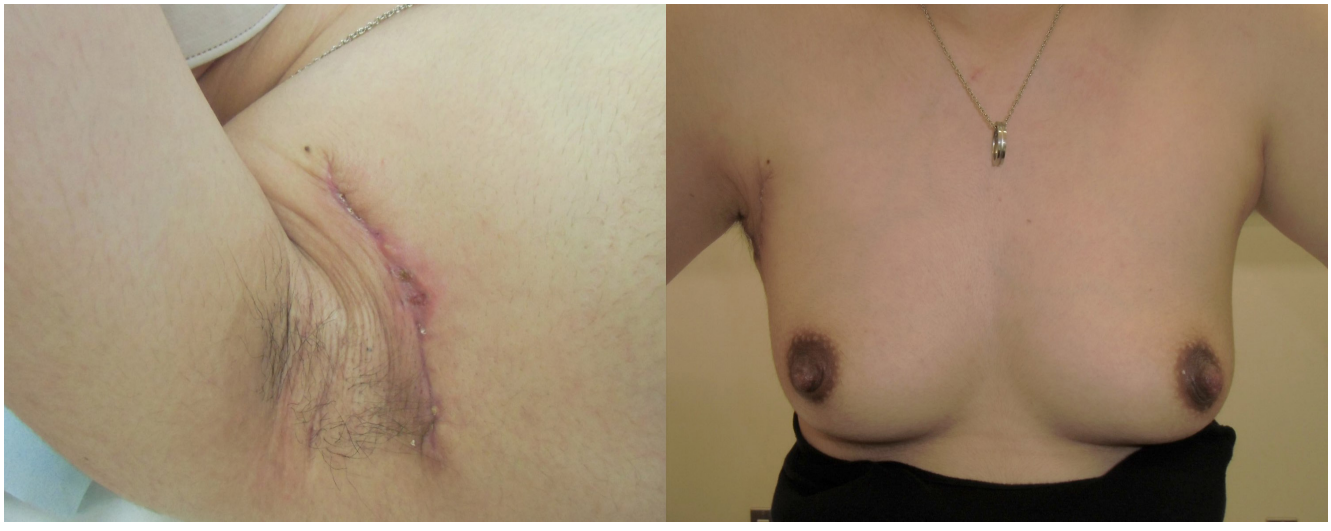

Figure 3. Images of the patient's right axilla (left) and breasts (right) 40 days after surgery

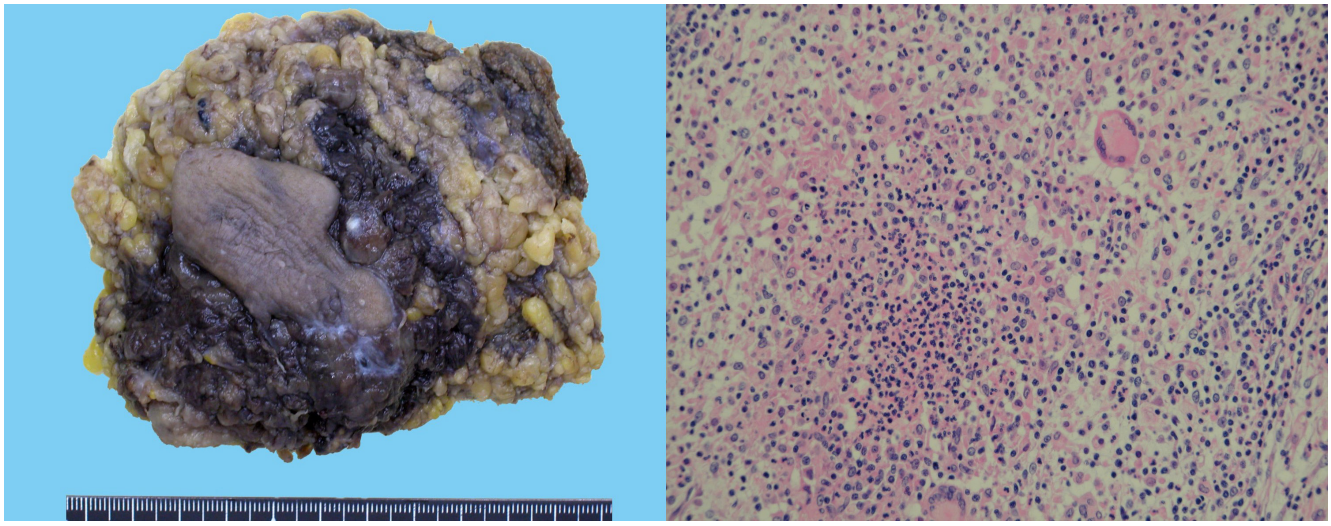

Figure 4. Excised mass (left) and pathological examination (right) showing granulation tissue with marked inflammatory cell infiltration, including polynuclear giant cells and abscess formation

consensus has been reached on the optimal dose and duration of treatment. This intervention can lead to a decrease in the diameter of the lesion, while adverse effects, such as Cushing syndrome, weight gain, hyperglycemia (1), and opportunistic infections are possible (8). Moreover, steroid treatment of GM during pregnancy has not been addressed to date. A few cases of GM during pregnancy were successfully treated with steroids (9, 10) but no information on adverse effects of the treatment and outcome of pregnancy were provided. Furthermore, it is suggested that exposure to steroids during early pregnancy increases the risk of oral cleft, premature delivery, and low birth weight (11, 12). Systemic steroid treatment and/or intralesional and topical steroid applications may have been alternatives in the present case, because our patient was in late pregnancy. However, in patients who are positive for *Corynebacterium* infection, as in the present case, steroid administration may facilitate relapse of GM through suppression of the host's immunity. It has also been demonstrated that patients with *Corynebacterium* infection tend to have longer treatment duration and higher risk of recurrence of complicated mastitis, compared with *Corynebacterium*-negative cases. Concurrent pregnancy and young age are both also associated with long treatment duration (13).

A recent meta-analysis comparing 138 cases of surgical treatment with 358 cases of steroid treatment demonstrated the superiority of the former (complete response rate: 90.6% vs. 71.8%; recurrence rate: 6.8% vs. 20.9%). Additionally, better results have been reported by combining surgery and steroid treatment, with a complete response rate of 94.5% and recurrence rate of 4.0% (14). Another meta-analysis showed that managing GM with steroids only may be less effective than a combination of steroids and surgery (15). Surgical procedures are associated with a different range of problems including stress and fear in patients, scarring and/or asymmetry of breast, and sometimes poorer cost-effectiveness. Furthermore, the main requirement for the surgical treatment option is that the lesion presents as a well-circumscribed mass. In diffuse lesions, it is not possible to excise the lesion while preserving the breast. In the present case, we selected surgical resection for the following reasons: (1) the patient was pregnant, and we were hesitant to use systemic steroid treatment; (2) bacterial culture was positive for *Corynebacterium* and steroid treatment would likely have been less effective; (3) the treatment period had already lasted for >2 months and the patient wanted early recovery; and (4) the lesion was in the axilla with a lesser impact on cosmesis.

In conclusion, there is no agreed standard management for GM. Therefore, treatment strategy should be planned on a case-by-case basis, taking into account the patient's situation. Unnecessary surgery should be avoided but early addition of surgical interventions may yield good outcomes, especially in pregnant women because of limited treatment options.

Acknowledgements

The authors thank Cathel Kerr, BSc, PhD, from Edanz Group (https://en-author-services.edanzgroup.com/ac) for editing a draft of this manuscript.

Informed Consent: The patient was informed that treatment results would be included in the study analysis.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: J.N., F.T., A.I.; Concept: J.N., K.O., K.S., A.I.; Design: J.N.; Data Collection and/or Processing: J.N.; Analysis and/or Interpretation: J.N.; Literature Search: J.N.; Writing: J.N.

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

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

References

1. Wolfrum A, Kümmel S, Theuerkauf I, Pelz E, Reinisch M. Granulomatous Mastitis: A Therapeutic and Diagnostic Challenge. Breast Care (Basel) 2018; 13: 413-418. (PMID: 30800035) [Crossref]
2. Parperis K, Achilleos S, Costi E, Vardas M. Granulomatous mastitis, erythema nodosum and arthritis syndrome: case-based review. Rheumatol Int 2021; 41: 1175-1181. (PMID: 33649961) [Crossref]
3. Paviour S, Musaad S, Roberts S, Taylor G, Taylor S, Shore K, et al. Corynebacterium species isolated from patients with mastitis. Clin Infect Dis 2002; 35: 1434-1440. (PMID: 12439810) [Crossref]

4. Pfeifer JD, Barr RJ, Wick MR. Ectopic breast tissue and breast-like sweat gland metaplasias: an overlapping spectrum of lesions. J Cutan Pathol 1999; 26: 190-196. (PMID: 10335896) [Crossref]
5. Yılmaz MA, Kaya TI, Demirel M, Yuyucu Karabulut Y. Pregnancy-associated granulomatous mastitis of accessory breast: A novel clinical presentation. Dermatol Ther 2021; 34: e14729. (PMID: 33381878) [Crossref]
6. Martinez-Ramos D, Simon-Monterde L, Suelves-Piqueres C, Queralt-Martin R, Granel-Villach L, Laguna-Sastre JM, et al. Idiopathic granulomatous mastitis: A systematic review of 3060 patients. Breast J 2019; 25: 1245-1250. (PMID: 31273861) [Crossref]
7. DeHertogh DA, Rossof AH, Harris AA, Economou SG. Prednisone management of granulomatous mastitis. N Engl J Med 1980; 303: 799-800. (PMID: 7191051) [Crossref]
8. Benson JR, Dumitru D. Idiopathic granulomatous mastitis: presentation, investigation and management. Future Oncol 2016; 12: 1381-1394. (PMID: 27067146) [Crossref]
9. Salesi M, Karimifar M, Salimi F, Mahzouni P. A case of granulomatous mastitis with erythema nodosum and arthritis. Rheumatol Int 2011; 31: 1093-1095. (PMID: 20012050) [Crossref]
10. Lucas R, Gussman D, Polis RL, Rattigan MI, Matulewicz TJ. Idiopathic granulomatous mastitis with erythema nodosum simulating breast abscess in pregnancy: A case report. Obstet Med 2014; 7: 37-39. (PMID: 27512418) [Crossref]
11. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet 1999; 86: 242-244. (PMID: 10482873) [Crossref]
12. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000; 62: 385-392. (PMID: 11091360) [Crossref]
13. Tsai MJ, Huang WC, Wang JT, Wang MY, Lee YH, Lin SW, et al. Factors associated with treatment duration and recurrence rate of complicated mastitis. J Microbiol Immunol Infect 2020; 53: 875-881. (PMID: 32327329) [Crossref]
14. Lei X, Chen K, Zhu L, Song E, Su F, Li S. Treatments for Idiopathic Granulomatous Mastitis: Systematic Review and Meta-Analysis. Breastfeed Med 2017; 12: 415-421. (PMID: 28731822) [Crossref]
15. Godazandeh G, Shojaee L, Alizadeh-Navaei R, Hessami A. Corticosteroids in idiopathic granulomatous mastitis: a systematic review and meta-analysis. Surg Today 2021; 51: 1897-1905. (PMID: 33590327) [Crossref]

Case Report

Eur J Breast Health 2022; 18(2): 199-202
DOI: 10.4274/ejbh.galenos.2021.2021-9-7

A Rare Case of Bilateral Synchronous Male Breast Cancer: A Multimodality Approach

Cihan Özgür[1], Baran Serdar Sunal[2], Nermin Tunçbilek[2]

[1]Clinic of Radiology, Bulanık State Hospital, Bulanık, Muş, Turkey
[2]Department of Radiology, Trakya University Faculty of Medicine, Edirne, Turkey

ABSTRACT

Breast cancer is a rare entity in men, accounting for less than 1% of all breast cancers. Contralateral breast cancer diagnosed within 12 months of the prior breast cancer is known as bilateral synchronous breast cancer. Bilateral, synchronous male breast cancer is extremely rare and consequently there are few publications describing imaging findings of synchronous bilateral male breast cancer. We aim to raise awareness about this rare entity by presenting the clinical and pathologic findings of a 64-year-old male case with synchronous bilateral breast cancer using multimodality imaging techniques including magnetic resonance imaging. Increasing awareness of the disease will prevent delays in diagnosis and treatment.

Keywords: Breast cancer; breast ultrasonography; magnetic resonance imaging; mammography; male breast cancer; synchronous neoplasms

Cite this article as: Özgür C, Sunal BS, Tunçbilek N. A Rare Case of Bilateral Synchronous Male Breast Cancer: A Multimodality Approach. Eur J Breast Health 2022; 18(2): 199-202

Key Points

- Mammography is the first-line method and is highly sensitive and specific for breast cancer in males, similar to female breast cancer.
- Magnetic resonance imaging can be used successfully in the assessment of the male breast and its use should be recommended, especially in cases where initial imaging is indeterminate.
- Increasing awareness of male breast cancer will prevent delays in diagnosis and treatment.

Introduction

Breast cancer is a rare entity in men, accounting for less than 1% of all breast cancers (1). Contralateral breast cancer diagnosed within 12 months of the prior breast cancer is known as bilateral synchronous breast cancer (2). Bilateral synchronous male breast cancer is extremely rare, constituting 0.5% to 2.5% of male breast cancers (3, 4). Bilateral synchronous involvement is less common than metachronous involvement (5). Risk factors include positive family history, increasing age, black race, BRCA2 mutations, radiation exposure, hyperestrogenic conditions (liver diseases, obesity, alcoholism, and estrogen treatment), hypoandrogenic and testicular conditions (Klinefelter's syndrome, undescended testis, orchitis, orchiectomy), and hyperprolactinemia (6). To the best of our knowledge, there are few publications describing imaging findings in bilateral synchronous male breast cancer. Here, the aim is to raise awareness about this rare entity by presenting the clinical, pathological, and radiological features of a 64-year-old male case with bilateral synchronous breast cancer.

Case Presentation

A 64-year-old male patient was admitted with complaints of swelling in both breasts and a painless palpable mass. The patient had no family history of breast cancer. Physical examination revealed increased volume in both breasts, bilateral hard immobile masses on palpation, and nipple retraction. The patient was referred for mammography (Selenia full field digital mammography system, Hologic, Bedford, MA, USA) and breast ultrasonography (US) (PLT-1005BT linear array transducer 5.0-14.0-MHz, Aplio 500 unit, Toshiba Medical Systems, Tokyo, Japan) examinations. Mammography showed a spiculated mass lesion in the retroareolar region of the right breast. An irregularly shaped and

Corresponding Author:
Cihan Özgür; cihanozguritf@gmail.com

Received: 21.09.2021
Accepted: 06.12.2021
Available Online Date: 01.04.2022

irregularly contoured mass with segmental, malign microcalcifications extending from the retroareolar region to the lower and inner quadrants was seen in the left breast (Figure 1). Left axillary and left interpectoral lymphadenopathy was noted. The mass lesions in both breasts were solid on US examination. The masses had multilobulated contours and a hypoechoic internal structure. The masses and both lymphadenopathies were found to be hypervascular on Doppler US (Figures 2 and 3).

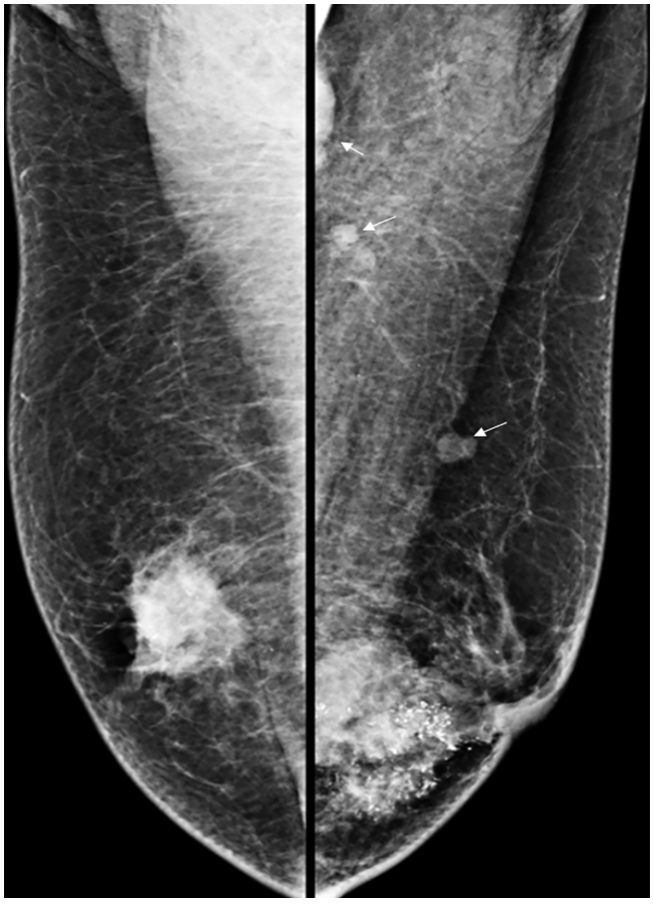

Figure 1. Mediolateral oblique mammography shows mass lesions in both breasts and left axillary and interpectoral lymphadenopathy (arrows)

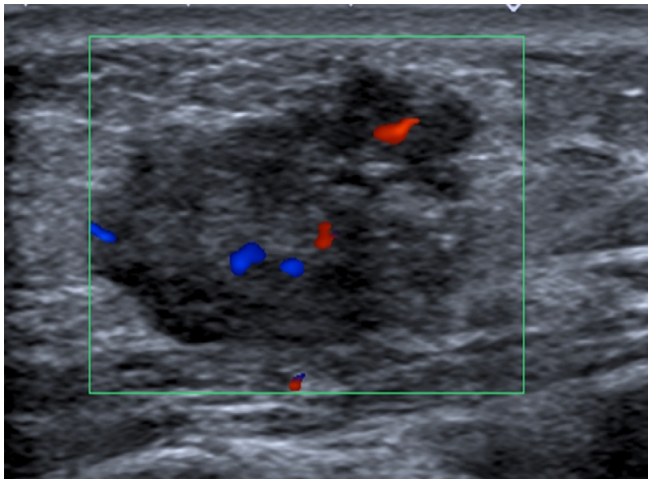

Figure 2. The mass lesion in the left breast was multilobular, hypervascular and had partly indistinct borders

Magnetic resonance imaging (MRI) was undertaken with T2, diffusion-weighted, precontrast and dynamic contrast-enhanced subtraction T1-weighted images with fat suppression sequences. MRI (1.5T MRI unit, Aera, Siemens Medical Systems, Enlargen, Germany) demonstrated bilateral malignant masses that had decreased signal intensity on the T2W image. The lesions demonstrated a malignant type of enhancement after administration of contrast material, with avid, early enhancement and a following uptake plateau (Figures 4 and 5). In addition, the mass in the right breast extended to the pectoral muscle. However, there was no signal change suggesting pectoral muscle invasion (Figure 6).

The patient subsequently underwent bilateral ultrasound-guided core needle biopsy (16 G Estacore Automatic Biopsy Needle, Geotek, Ankara, Turkey), revealing pathology consistent with the lesions to be moderately differentiated invasive ductal carcinoma. Immunohistochemical examination revealed a progesterone receptor-positive (70%), estrogen receptor-positive (90%) carcinoma with Ki-67 index of 30%. Human epidermal growth factor receptor 2 (HER-2) status of the tumor was equivocal (score +2). Preoperative genetic testing revealed the patient to be negative for mutations in the breast cancer 1 (*BRCA1*) and breast cancer 2 (*BRCA2)* genes. The

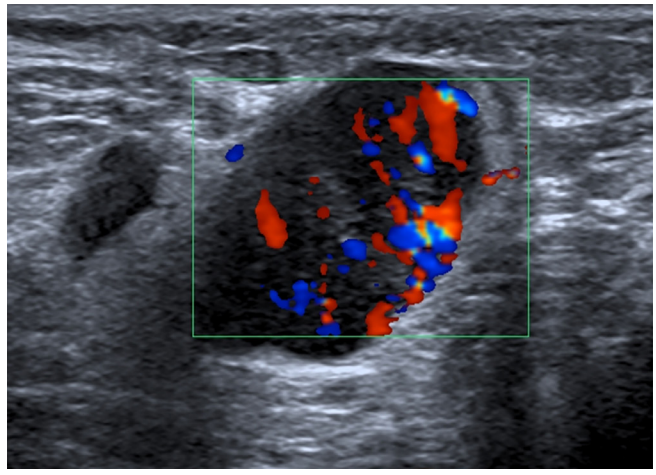

Figure 3. On Doppler ultrasonography, axillary lymphadenopathy was hypervascular

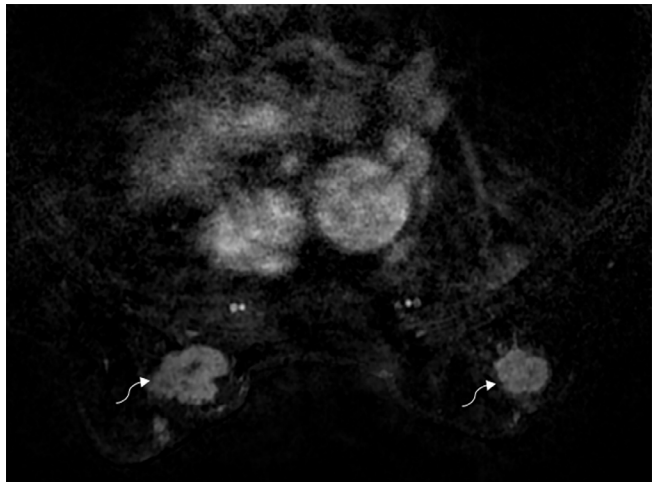

Figure 4. Hypervascular mass lesions are evident on dynamic, contrast-enhanced subtraction T1-weighted magnetic resonance images with fat suppression (curved arrows)

patient underwent bilateral mastectomy and axillary dissection after neoadjuvant chemotherapy. Neoadjuvant chemotherapy response was evaluated with contrast-enhanced MRI (not shown because imaging was performed at another center), and a complete response in the right breast and a partial response in the left breast was observed. Complete response was obtained in the right breast and axilla after neoadjuvant chemotherapy and no tumor focus was detected on subsequent postoperative histopathological examination. A tumor focus of 6 mm in diameter was seen in the left breast with a Ki-67 index of 4%. However, the focus was strongly positive for both progesterone receptor (90%) and estrogen receptor (90%). Metastasis was detected in one lymph node in the left axilla. Adjuvant external radiation therapy and tamoxifen were given. The patient was followed up with US and thoracoabdominal computed tomography (CT). The patient was disease-free during one-year of follow-up.

Discussion and Conclusion

The lifetime risk for breast cancer in men is about 1:1000 (7). Male breast cancers differ from female breast cancers in some aspects. The mean age at diagnosis is 67 years, which is 5 years older than women. The mean tumor size is usually greater, and nodal involvement, androgen, and estrogen receptor positivity are more common in male breast cancers (8-10). The most common type of breast cancer is invasive carcinoma, and the most common histological type is invasive ductal carcinoma (11). Survival is lower in patients who are elderly at the time of diagnosis, have advanced disease, and have triple-negative cancer than in those who do not have these characteristics (12). Painless retro-areolar mass, nipple retraction, bloody nipple discharge, skin ulceration, and palpable axillary lymphadenopathy are the most common signs in male breast cancer (13). Imaging findings in male breast cancers are similar to those of females. However, the literature on the use of MRI in male cases is limited. The imaging findings in our case were compatible with the literature. Although the routine use of MRI in male breast cancer cases is not recommended, it may provide significant benefit in selected cases, especially in cases with axillary lymphadenopathy in which US and mammography are negative, in the evaluation of neoadjuvant chemotherapy, chest wall involvement, and postoperative residual evaluation (14). Since randomized prospective studies have not been conducted due to the rarity of the disease, treatment approaches are based on the treatment approaches in female breast cancer cases. Unlike breast-conserving approaches in female patients with early-stage breast cancer, the tendency to perform mastectomy and axillary lymph node dissection/sentinel lymph node biopsy are more common in male breast cancer cases (15). In contrast to earlier reports, our case highlights the role of neoadjuvant chemotherapy in male breast cancer treatment. Breast cancer in males is diagnosed at a later stage due to factors including a lack of screening programs due to non-cost-effectiveness, low awareness, and less breast tissue in men compared to women (6). Increasing awareness of the disease among clinicians will prevent delays in diagnosis and treatment.

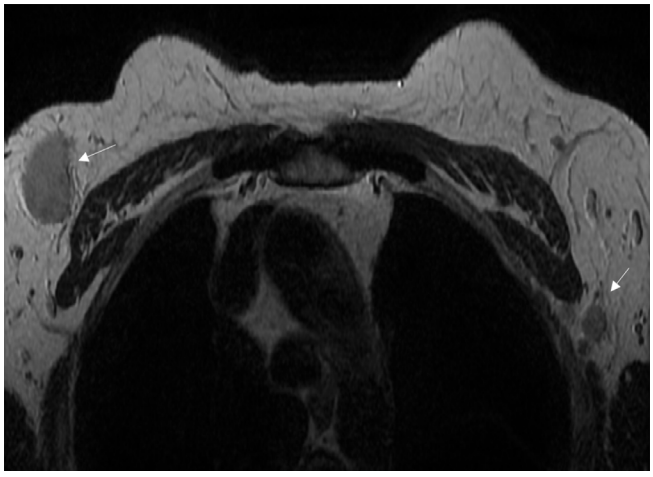

Figure 5. Bilateral axillary lymphadenopathies are seen on the T2-weighted magnetic resonance image

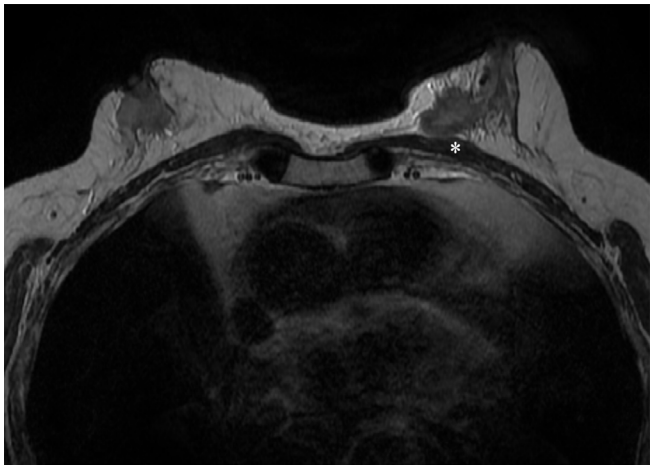

Figure 6. Although the right breast mass extended posteriorly to the pectoral muscle, there was no signal change, suggesting an absence of muscle invasion (asterisk)

Informed Consent: It was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: C.Ö., N.T.; Design: C.Ö., N.T.; Data Collection and/or Processing: B.S.S.; Analysis and/or Interpretation: N.T.; Literature Search: C.Ö., B.S.S.; Writing: C.Ö.

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

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

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017; 67: 7-30. (PMID: 28055103) [Crossref]
2. Al-Jurf AS, Jochimsen PR, Urdaneta LF, Scott DH. Factors influencing survival in bilateral breast cancer. J Surg Oncol 1981; 16: 343-348. (PMID: 7253654) [Crossref]
3. Nwashilli NJ, Ugiagbe EE. Bilateral synchronous male breast cancer. Saudi Med J 2015; 36: 359-362. (PMID: 25737181) [Crossref]
4. Sosnovskikh I, Naninato P, Gatti G, Caldarella P, Masullo M, De Brito LL, et al. Synchronous bilateral breast cancer in men: a case report and review of the literature. Tumori 2007; 93: 225-227. (PMID: 17557578) [Crossref]
5. Coard K, McCartney T. Bilateral synchronous carcinoma of the male breast in a patient receiving estrogen therapy for carcinoma of the prostate: cause or coincidence? South Med J 2004; 97: 308-310. (PMID: 15043344) [Crossref]

6. Weiss JR, Moysich KB, Swede H. Epidemiology of male breast cancer. Cancer Epidemiol Biomarkers Prev 2005; 14: 20-26. (PMID: 15668471) [Crossref]

7. Yalaza M, İnan A, Bozer M. Male Breast Cancer. J Breast Health 2016; 12: 1-8. (PMID: 28331724) [Crossref]

8. Doebar SC, Slaets L, Cardoso F, Giordano SH, Bartlett JM, Tryfonidis K, et al. Male breast cancer precursor lesions: analysis of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Mod Pathol 2017; 30: 509-518. (PMID: 28084333) [Crossref]

9. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN. Breast carcinoma in men: a population-based study. Cancer 2004; 101: 51-57. (PMID: 15221988) [Crossref]

10. Greif JM, Pezzi CM, Klimberg VS, Bailey L, Zuraek M. Gender differences in breast cancer: analysis of 13,000 breast cancers in men from the National Cancer Data Base. Ann Surg Oncol 2012; 19: 3199-3204. (PMID: 22766989) [Crossref]

11. 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]

12. Leone JP, 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]

13. 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]

14. Shin K, Martaindale S, Whitman GJ. Male breast magnetic resonance imaging: when is it helpful? Our experience over the last decade. Curr Probl Diagn Radiol 2019; 48: 196-203. (PMID: 29454681) [Crossref]

15. Cardoso F, Bartlett JMS, Slaets L, van Deurzen CHM, van Leeuwen-Stok E, Porter P, et al. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Ann Oncol 2018; 29: 405-417. (PMID: 29092024) [Crossref]

Letter to the Editor

Eur J Breast Health 2022; 18(2): 203-204
DOI: 10.4274/ejbh.galenos.2022.2022-2-3

Will Radiomics Replace Sentinel Lymph Node Biopsy?

Abdullah S. Eldaly[1], Ayman R. Fath[2], Sarah M. Mashaly[3]

[1]Division of Plastic Surgery, Mayo Clinic, Florida, USA
[2]Department of Internal Medicine, Creighton University Arizona Health Education Alliance, Arizona, USA
[3]Department of Dermatology and Venereology, El-Menshawy General Hospital, Tanta, Egypt

Cite this article as: Eldaly AS, Fath AR, Mashaly SM. Will Radiomics Replace Sentinel Lymph Node Biopsy? Eur J Breast Health 2022; 18(2): 203-204

Dear Editor,

Axillary lymph node metastasis is by far the most vital determinant of survival for breast cancer patients (1). Sentinel lymph node biopsy (SLNB) is the gold standard for axillary lymph node staging in clinically node-negative patients. However, despite the reported high sensitivity (44%–100%) and specificity (100%) of SLNB (2), it is associated with multiple morbidities, including sensory impairment, motor dysfunction, and lymphedema (3).

Radiomics is a new type of specialized artificial intelligence that extracts specific features from medical images to construct a disease-specific model, known as a radiomics signature, that is then used to predict disease status in other images (4). Radiomics workflow can be summarized in four cardinal steps: manual or automatic segmentation; feature extraction with specialized tools; selection of the most relevant features using machine learning methods; and radiomics analysis to build the predictive model (4).

Many studies have used radiomics to predict axillary lymph node status in breast cancer patients. Magnetic resonance imaging, computed tomography, and mammography are usually used as the image sources to build the predictive model. The results of radiomics are promising, with an accuracy, sensitivity, and specificity as high as 98% (5).

Although radiomics shows high accuracy in predicting axillary lymph node metastasis, it is not expected to replace SLNB in the near future. This is because the evidence from current radiomics studies is of modest quality. To date, almost all radiomics studies are retrospective in design and lack comparison with the gold standard. Moreover, most of the studies lack external validation and cost-effectiveness analysis.

We believe that replacing SLNB with radiomics in axillary lymph node staging in breast cancer is possible and will spare millions of patients unnecessary surgical interventions. However, implementing radiomics in breast cancer care requires robust evidence from randomized controlled trials. Whether or not the current evidence from the retrospective studies justifies clinical trials is yet to be determined. The answer to this question may be solved by conducting a meta-analysis of the existing literature.

Keywords: Artificial Intelligence; Axillary lymph node metastases; cancer; machine learning; prediction; radiomics

Corresponding Author:
Abdullah S. Eldaly; Eldaly.Abdullah@mayo.edu; abdullaheldali@gmail.com

Received: 09.02.2022
Accepted: 19.02.2022
Available Online Date: 01.04.2022

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.S.E; Design: A.R.F.; Data Collection and/or Processing: S.M.M.; Analysis and/or Interpretation: A.S.E.; Literature Search: A.R.F.; Writing: A.S.E.

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

Financial Disclosure: The authors declare that this study received no financial Disclosure.

References

1. Beenken SW, Urist MM, Zhang Y, Desmond R, Krontiras H, Medina H, et al. Axillary lymph node status, but not tumor size, predicts locoregional recurrence and overall survival after mastectomy for breast cancer. Ann Surg 2003; 237: 738-739. (PMID: 12724640) [Crossref]
2. Tew K, Irwig L, Matthews A, Crowe P, Macaskill P. Meta-analysis of sentinel node imprint cytology in breast cancer. Br J Surg 2005; 92: 1068-1080. (PMID: 16106479) [Crossref]
3. McLaughlin SA, Wright MJ, Morris KT, Giron GL, Sampson MR, Brockway JP, et al. Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. J Clin Oncol 2008; 26: 5213-5219. (PMID: 18838709) [Crossref]
4. Mayerhoefer ME, Materka A, Langs G, Häggström I, Szczypiński P, Gibbs P, et al. Introduction to Radiomics. J Nucl Med 2020; 61: 488-495. (PMID: 32060219) [Crossref]
5. Ashiba H, Nakayama R. Computerized evaluation scheme to detect metastasis in sentinel lymph nodes using contrast-enhanced computed tomography before breast cancer surgery. Radiol Phys Technol 2019; 12: 55-60. (PMID: 30499048) [Crossref]