E-ISSN 2587-0831

eurjbreasthealth.com

European Journal of Breast Health

Indexed in PubMed Central and Web of Science - ESCI

VOLUME: 20 • ISSUE: 4 • OCTOBER 2024

EUROPEAN JOURNAL OF BREAST HEALTH

SYSTEMATIC REVIEW

ORIGINAL ARTICLES

CASE REPORTS

Turkish Federation of Breast Diseases Societies

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

The Senologic International Society (SIS) and the National Consortium of Breast Centers (NCBC) are the official supporters of the journal.

SIS ISS SENOLOGIC INTERNATIONAL SOCIETY INTERNATIONAL SCHOOL OF SENOLOGY

NCBC National Consortium of Breast Centers

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

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Turkey
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr

Publisher Certificate Number: 14521
Online Publication Date: October 2024
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, Scopus.

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 (530) 177 30 97

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 (530) 177 30 97

E-mail : info@galenos.com.tr

Web : www.galenos.com.tr

European Journal of Breast Health

Contents

SYSTEMATIC REVIEW

ORIGINAL ARTICLES

European Journal of Breast Health

Contents

CASE REPORTS

INDEX

Systematic Review

Eur J Breast Health 2024; 20(4): 233-240
DOI: 10.4274/ejbh.galenos.2024.2024-5-2

The Use of Intralesional Corticosteroids in Idiopathic Granulomatous Mastitis: A Systematic Review

Asel Wijesinghe[1], Kasun Lakmal[2], Jeewantha Senevirathna[2], Bhanu Wijetilake[1], JLTK. Fernando[1], Umesh Jayarajah[3], Ajith De Silva[4], Kanchana Wijesinghe[1]

[1]Department of Surgery, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka
[2]University of Surgical Unit, Colombo South Teaching Hospital, Colombo, Sri Lanka
[3]Department of Surgery, Faculty of Medicine, Colombo, Sri Lanka
[4]Department of Surgery, National Hospital of Sri Lanka, Colombo, Sri Lanka

ABSTRACT

Idiopathic granulomatous mastitis (IGM) is a debilitating, chronic, inflammatory condition of the breast. Several studies have emerged evaluating intralesional steroid (ILS) injection and topical steroid administration as a treatment for IGM. However, there is a dearth of international consensuses with regards to the management of IGM. Therefore, we have systematically reviewed the effectiveness of ILS in the management of IGM. A systematic search was conducted in PubMed and Cochrane Library databases, the Google Scholar website and by citation searching up to June 15th, 2023. Eight articles were selected and analyzed. A total of 397 IGM patients were included in the review. The mean patient age was 35.7 years, ranging from 23–62 years. The mean pre-treatment diameter of lesions was 27.5 mm. A total of 184 patients were treated with ILS. The mean complete clinical response time was 2.6 months. The overall complete response rate was 92.8%. Complications following ILS were minor, with hematoma, skin atrophy and hyperemia being commonly described, while avoiding the systemic side effects of oral steroid use, such as weight gain and hirsutism, which were the most commonly reported side effects with oral steroids. The recurrence rates in the ILS group (6.6%) appear to be lower than in the oral steroid group (25.8%) and surgery group (26.3%). ILS seem to show a favorable outcome in terms of complete response rate, complete clinical response time and has a lower recurrence rate and complication rate when compared to other intervention strategies. However, more comparative studies with standardized protocols are necessary to ascertain the optimum type, dosage and frequency of ILS regimens.

Keywords: Idiopathic granulomatous mastitis; corticosteroids; intralesional steroid

Cite this article as: Wijesinghe A, Lakmal K, Senevirathna J, Wijetilake B, Fernando JLTK, Jayarajah U, De Silva A, Wijesinghe K. The Use of Intralesional Corticosteroids in Idiopathic Granulomatous Mastitis: A Systematic Review. Eur J Breast Health. 2024; 20(4): 233-240

Key Points

- Idiopathic granulomatous mastitis (IGM) is a debilitating chronic inflammatory condition of the breast.
- Intralesional steroid injection has become a promising treatment option for IGM.
- However, there is a dearth of international consensuses with regards to the management of IGM.
- This study is a systematic review of the effectiveness of intralesional steroids in the management of IGM to help understand the usage and efficacy of intralesional steroids.

Introduction

Idiopathic granulomatous mastitis (IGM) is a rare, chronic, benign inflammatory condition of the breast which commonly affects women of childbearing age with a history of breastfeeding (1). Infrequently, IGM has been reported in nulliparous women (2) and in men (3). The condition was first described in 1972 (4). Women from Southeast Asia and the Middle East may have a higher incidence of IGM than those of European descent (5). It has also been shown that IGM is commoner in those of Hispanic ethnicity (6).

Despite being described in the literature for over 50 years, the possible etiology for IGM remains elusive. Pregnancy, hyperprolactinemia (7), *Corynebacterium* infections (8), reactions caused by oral contraceptives and autoimmune reactions (9) seem to be associated with IGM. The strong link between IGM and lactation may be due to micro-trauma caused by milk stasis and breastfeeding (1).

Patients with IGM commonly present with a breast mass, pain, redness, peau d'orange appearance and axillary lymph node enlargement (10, 11). Radiologically, ultrasound features include circumscribed heterogeneous hypoechoic masses with tubular formations, while the commonest mammography findings are focal or diffuse asymmetrical density (12, 13). Magnetic resonance imaging is not routinely used in the workup of IGM (12, 13). Importantly, IGM is indistinguishable

Corresponding Author:
Kanchana Wijesinghe; kwijesinghe@sjp.ac.lk

Received: 14.05.2024
Accepted: 09.06.2024
Available Online Date: 26.09.2024

from malignancy both clinically and radiologically (14) and can only be reliably diagnosed by histopathological examination of a biopsy (1).

There is a dearth of international consensuses with regards to the management of IGM. Although it may be self-limiting, with observation alone leading to complete resolution within 5–20 months (15), the morbidity, persistence and progression of the condition in some, especially those with large (>5 cm), bilateral lesions or lesions complicated by abscesses and fistulae may necessitate intervention (16). Etiology-specific treatment, such as bromocriptine for hyperprolactinemia and antibiotics for *Corynebacterium* infection, have been described (17). Surgical measures, though effective, are plagued with adverse outcomes, such as scarring, poor wound healing, recurrence, fistula formation and mastectomy (18) and is generally limited to those with refractory or recurrent disease (17).

Oral steroid (OS) use in the management of IGM was first described in 1980 and acts by mitigating inflammation and autoimmune reactions that may be a causative factor in IGM (19). Oral steroids have been shown to reduce the extent of surgery, or even alleviating the need for surgery in selected cases (17). Therefore, OS is generally considered a first line treatment option. However, its use is associated with side effects such as Cushing syndrome, weight gain, hyperglycemia and opportunistic infections (1).

Methotrexate (MTX) has also been described as a steroid sparing agent in the treatment of IGM, but its efficacy is controversial and its adverse effect profile, especially among women of reproductive age, amongst whom this disease is commonest, has resulted in limited use of this treatment modality (17).

Intralesional steroid (ILS) use was first described for the management of IGM in 2012 by Munot et al. (19) amongst a cohort of four subjects, all of whom showed a complete response, with no local or systemic side effects and no recurrence within a year of treatment. This initial success sparked an interest in the use of this novel method, and several studies have emerged evaluating ILS injection and topical steroid administration as a treatment for IGM. The results seem promising but there is heterogeneity within the published studies.

Therefore, this systematic review was conducted to assess the efficacy of this treatment, as it potentially mitigates the adverse effects of surgery and OS use. We have systematically reviewed the effectiveness of intralesional corticosteroids in the management of IGM.

This study has been registered in PROSPERO on 10.08.2023. ID: CRD42023449788.

Materials and Methods

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline was used for the study design, search strategy, screening, and reporting. A systematic search was conducted using MeSH keywords as follows: (All available MeSH terms for "steroids") AND "idiopathic granulomatous mastitis" AND "intralesional" in the PubMed and Cochrane Library databases, the Google Scholar website and by citation searching up to June 15th, 2023. Only publications in English and human interventional studies were included.

Study Selection Criteria

Studies were independently selected by two members of the research group. In case of disagreement, a discussion was held between the two and the third member until the matter was resolved. The following criteria were used to include studies in this systematic review: (1) human studies which used intra-lesional corticosteroids to treat IGM, (2) studies confirming IGM by histopathological diagnosis, and (3) studies reporting complete clinical response rates. Studies were excluded if they were case reports or case series without individual outcome data, review articles, conference abstracts, letters, animal studies, or *in vitro* studies; duplicate publications; or if the desired parameters such as complete clinical response rate were not reported.

The literature search protocol is summarized in Figure 1.

Data Extraction and Quality Assessment

Two members of the group independently assessed the quality of each selected study and extracted data from the papers and results were compared. Any conflicts were discussed and resolved with a third investigator. The data extraction checklist included the name of the first author, period of data collection, year of publication, country where the study was performed, type of study, number of patients in each intervention, mean age, location of lesion (s), clinical presentation, the type, dose, frequency and duration of intralesional and/or OS use, evaluation frequency and mean follow-up time, complete clinical response rate, mean complete response time period, the number and types of adverse effects and the complication rate of each intervention.

Quality Assessment

The modified downs and black scale (20) was used to assess the quality of the included studies. A 27-point scale was used and was categorized as follows; Excellent (26–27), Good (20–25), Fair (15–19) and Poor (≤14). All studies achieved a "Fair" or greater score and were included in the systematic review (Table 1).

Data Analysis

Data were analyzed based on subgroups of patients classified according to treatment modalities used and were classified as the ILS group (Group 1), OS group (Group 2), Surgery Group (Group 3) and Combined Therapy Group (Group 4). In addition, patients who were given OS in addition to ILS for only a short duration and for whom individual outcome data was not published were included in the ILS group.

Complete response was defined >90% clinical resolution, based on a previous study (21).

Recurrence was defined as clinical re-emergence of lesions following complete or partial response.

Continuous variables are presented as mean with minimum and maximum values, and categorical variables as numbers and percentages. All missing information, including outcome data in patients lost to follow-up was considered as such, and no assumptions were made. Patients with missing data for a specific variable were not included in the statistical analysis.

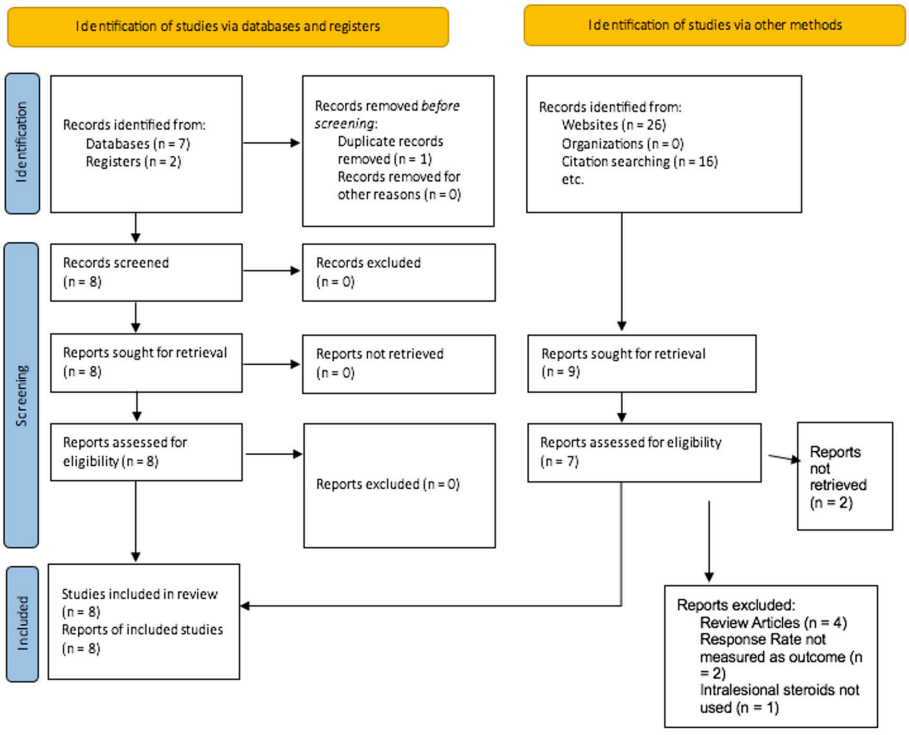

Figure 1. PRISMA flowchart

Table 1. Characteristics of studies included in systematic review

Study	Country	Type of study	Number of patients	Number treated with ILS	Number treated with OS	Number treated with surgery	Number treated with combination/ observation	Quality assessment*
Alper et al. (22) 2020	Turkey	Prospective cohort	28	28	0	0	0	Fair (15/27)
Ertürk et al. (23) 2022	Turkey	Retrospective descriptive	86	38	0	48	0	Fair (19/27)
Karami et al. (21) 2022	Iran	Randomized clinical trial	99	31	30	0	38 (Combination)	Good (23/27)
Kim et al. (24) 2016	South Korea	Retrospective descriptive	15	15	0	0	0	Fair (16/27)
Tang et al. (25) 2020	USA	Retrospective descriptive	49	12	0	9	28 (Observation)	Fair (17/27)
Toktas et al. (26) 2021	Turkey	Retrospective descriptive	78	46	32	0	0	Good (20/27)
Toktas and Toprak (27) 2021	Turkey	Retrospective descriptive	6	6	0	0	0	Fair (15/27)
Yildirim et al. (28) 2021	Turkey	Randomized clinical trial	36	17	19	0	0	Good (23/27)

*Downs and black scale was used for quality assessment; ILS: Intralesional steroid; OS: Oral steroid

Results

Description of Studies

Eight studies were selected that included 397 IGM patients and were analyzed for this review. The mean (range) patient age was 35.7 (23–62) years. The mean pre-treatment diameter of lesions was 27.5 (22.2–37.2) mm. Bilateral or multifocal disease was noted in only a minority (11.9%). The mean duration of symptoms upon presentation was 7.8 months. The majority presented with a painful mass, with or without features of inflammation. Other notable presentations included firmness of skin and soft tissue changes, such as purulence, abscesses, ulceration, and fistulation. The mean follow-up frequency was 4.7 weeks while the mean follow-up time was 12.4 months. The characteristics of studies included in this review are given in Table 1.

Intra-Lesional Steroid Group (Group 1)

All studies (21–28) contained an ILS subgroup. A total of 193 (48.6%) patients were treated with ILS of which 9 were lost to follow-up in one study (26), hence the outcome data was not available, and was thus calculated for 184 patients with outcome data. The number of ILS dosages ranged from 1–7 injections. The frequency of dosing was 1-weekly in two studies, 2-weekly in two studies, 4-weekly in three studies, while one study had a single dosage regimen only. Most studies (5/8; 62.5%) used triamcinolone as the ILS, while two studies used methylprednisolone, and a single study used betamethasone disodium phosphate. In one study (24), oral prednisolone (10 mg daily) was combined in 5 patients with multiple, large, or painful abscesses in the early period, before ILS was an established treatment modality. This heterogeneity of ILS regimens was based on common denominators such as the severity, number, and size of the lesions. Additionally, three studies used topical steroids for one month, of which two used triamcinolone and one used prednisolone. A summary of ILS treatment regimens used in the studies included in this review is given in Table 2.

The mean complete clinical response time was 2.6 months. The overall complete response rate was 92.8% (n = 171), while the partial response rate was 6.0% (n = 11). There were only 2 non-responders in this group. The recurrence rate during the respective periods of follow-up was 6.6% (n = 11) (21-27). In one study (23), the two partial responders were followed up without active intervention and the lesions remained stable throughout the follow-up period. In another study (26), one non-responder underwent total mastectomy due to diffuse multifocal disease. The outcomes of the remaining partial responders, non-responders and recurrences were not reported. Seven patients (3.8%) reported minor complications following local steroid therapy. Three patients (0.8%) reported skin atrophy, 2 patients (0.5%) reported hematoma and two patients (0.5%) reported skin hyperemia as adverse effects. These side effects were observed in study groups prescribing topical and ILS as well as ILS-only group and were only observed in groups using Triamcinolone as the intra-lesional steroid.

Oral Steroid Comparative Group (Group 2)

Three studies contained a comparative OS subgroup, which provided outcome data (21, 26, 28). Accordingly, 81 (20.4%) patients who were treated solely with OS were included in this subgroup.

Two studies used oral methylprednisolone (26, 28), while the third study used prednisolone (21). The third study (21) also used oral MTX 10 mg per week for 1 month then 15 mg weekly until prednisolone was discontinued. In addition, daily Calcium-D and folic acid supplements were given to all patients in the third study.

The dosage of OS was heterogenous, with one study giving a fixed dose of 32 mg, the second study dosing based on the size, number of lesions and bodyweight (Unilateral, single lesions less than 5 cm: 0.5 mg/kg/day; bilateral, multiple or lesions exceeding 5 cm or with ulceration: 1 mg/kg/day), while the third study gave a tapering OS dose (50 mg/day for two weeks followed by 25 mg/day for 1 month, then 12.5 mg/day 1 month, then 10 mg/day for 1 month and 5 mg/day for 1 month for a total of 4 months, 2 weeks). All three studies had daily dosing regimens.

The total duration of dosage was 1 month in the first and second studies (with an additional 1 month of dosage in 5 patients with no response in the second study), and 4 months and 2 weeks in the third study.

A summary of OS treatment regimens used in the studies included in this review is given in Table 3. The mean complete response time was

Table 2. Intra-lesional steroid regimes used in studies included in the systematic review

Study	ILS type	ILS single dose (mg)	Dosage range	Total dosage range (mg)	Frequency of dosage	Topical steroid use
Alper et al. (22) 2020	Methylprednisolone acetate	40	2–7	80–280	3–4 weekly	No
Toktas and Toprak (27) 2021	Methylprednisolone acetate	40	1–2	40–80	2-weekly	0.125% prednisolone twice a day, EOD for 1 month
Ertürk et al. (23) 2022	Triamcinolone acetonide	40–80	1–5	40–400	4-weekly	Triamcinolone Daily - 1 month (after ILS)
Kim et al. (24) 2016	Triamcinolone acetonide	40	2–6	80–240	1–2 weekly	No
Tang et al. (25) 2020	Triamcinolone acetonide	80–160	1	80–160	Single dose	No
Toktas et al. (26) 2021	Triamcinolone acetonide	20 mg	1–3	20 mg up to 3 times	4-weekly	Triamcinolone acetonide 0.1%, twice a day, EOD for 1 month
Yildirim et al. (28) 2021	Triamcinolone acetonide	40	1–5	40–200	1 weekly	No
Karami et al. (21) 2022	Betamethasone disodium phosphate + betamethasone acetate	6	1–4	6–24	1 weekly	No

ILS: Intralesional steroid

reported as 6.36 months (range; 6–9) in one study (21). The overall complete response rate was 86.4% (n = 70), with 4 patients (4.9%) showing a partial clinical response. The non-response rate was 8.6% (n = 7). Recurrence data was available in two studies (21, 26), with the overall recurrence rate in complete and partial responders in the two studies being 25.8% (n = 16). Notably, 93.8% (n = 15) of recurrences occurred in the study not using MTX (26). In one study (26), 5 patients with complete response who then developed recurrence were treated with successive doses of oral steroids, while surgery was performed on 4 patients with no response or recurrent disease including lumpectomy (n = 3) and mastectomy (n = 1) for diffuse disease. The final outcome of partial responders, non-responders and recurrences were not reported in the other two studies. The overall complication rate was 9.9% (n = 8) following OS therapy, with systemic side effects such as weight gain (n = 3) and hirsutism (n = 2).

Surgery Group (Group 3)

Two studies had cohorts that were treated exclusively with surgery (23, 25). A total of 57 (14.4%) patients were treated with surgery only. The majority underwent local excision (91.2%, n = 52) and only 5 (8.8%) patients required mastectomy. Only one study (23) reported a recurrence rate after surgery, which was 31.2% (n = 15/48), and this was reported at a 12-month follow-up after surgery. The same study (23) reported a complication rate of 8.3% (n = 4), of which three were surgical site infections and one was a hematoma. This study also noted that post treatment median pain score was significantly higher in patients who underwent surgery compared to those who underwent ILS therapy (p<0.001). Notably, the aesthetic outcome of surgery was not assessed in either study.

Combined Group (Group 4)

A single study described a cohort with a combination of oral and ILS with outcome data (21). In this study, patients received intralesional betamethasone acetate (3 mg) and betamethasone disodium phosphate (3 mg/mL) in a weekly dosage between 1–4 times, combined with a tapering dose of oral prednisolone (50 mg/day for two weeks, followed by a taper to 5 mg/day in 4 months: 25 mg/day for 1 month followed by 12.5 mg/day 1 month, then 10 mg/day for 1 month and 5 mg/day for 1 month) and weekly doses of oral MTX (10 mg per week for 1 month then 15 mg per week until prednisolone was discontinued).

A total of 38 (9.6%) of patients were treated with combined therapy. The mean complete response time was 4.33 months (range: 1–6). The complete clinical response rate was 89.5% (n = 34). Two patients (5.3%) had a partial clinical response, while 2 more patients were non-responders. Five patients (13.2%) were documented to have recurrence in the combined subgroup. Four patients (10.5%) had systemic complications following combined therapy.

Comparison of Outcomes in the ILS Group

Due to the heterogeneity of the studies, as discussed below, a comprehensive meta-analysis of the efficacy of the ILS regimens is not feasible. However, preliminary comparisons were carried out in this study.

The complete response rates of studies using Methylprednisolone (91.2%), Triamcinolone (94.1%) and Betamethasone (90.3%) appear to be similar. The recurrence rate of the single study (21) that used Betamethasone (19.4%) appears to be higher than that of studies that used Methylprednisolone (2.9%) and Triamcinolone (3.4%). Also, studies that used Triamcinolone were the only studies that reported local complications (n = 7). Three patients (42.9%) reported skin atrophy, 2 patients (28.6%) reported hematoma and 2 patients (28.6%) reported skin hyperemia as adverse effects. The comparison of each type of ILS is summarized in Table 4.

The comparison of the outcomes of each group are detailed in Table 5.

Discussion and Conclusion

In this systematic review, we analyzed eight studies that used ILS. Methylprednisolone, Triamcinolone, Betamethasone and Prednisolone were the steroids used. ILS use is defined as the administration of

Table 3. Oral steroid regimes used in studies included in systematic review

Study	Number of patients treated with Oral steroid	Oral steroid type	Oral steroid dose	Frequency of dosage	Duration of treatment (months)
Karami et al. (21) 2022	30	Prednisolone	Tapering dose of 50 to 5 mg	Daily	4.5
Toktas et al. (26) 2021	32	Methylprednisolone	32 mg	Daily	1
Yildirim et al. (28) 2021	19	Methylprednisolone	0.5–1 mg/kg/day based on lesion characteristics	Daily	1–2

Table 4. Comparison of outcomes of intra lesional steroid group

Steroid type	Total treated	Complete response no	Complete response rate (%)	Recurrence no	Recurrence rate (%)	No of complications	Complication rate (%)
Methylprednisolone	34	31	91.2	1	2.9	0	0
Triamcinolone	119	112	94.1	4	3.4	7	5.9
Betamethasone	31	28	90.3	6	19.4	0	0
Total	184	171	92.9	11	6.0	7	3.8

steroids directly into a lesion, thereby bypassing the metabolic first pass effects and reducing the well-known systemic adverse effects of steroids, such as hypertension, osteoporosis, gastrointestinal disturbances, weight gain and diabetes mellitus (29), and allowing higher doses to be used (30). This technique creates a subepidermal depot which bypasses the superficial barrier zone (31). The use of ILS was first described in the management of dermatoses in 1961 (32). Since then, a variety of dermatological, rheumatological and surgical uses have been described.

ILS has a wide range of applications in dermatology and the dose per session generally depends on the size of the skin lesions, while the number of treatments depends on many clinical factors, including the disease, site of lesions, age of the patient and response to previous injections. The duration between treatment sessions is around 3–6 weeks (33). A similar rationale to that used in dermatological conditions was observed in the dosing regimens of the studies that used ILS in the management of IGM.

Comparison of Efficacy

In all eight studies, we noted a heterogeneity in the prescription of steroids with varying potencies, dosage, and frequencies. The basis for steroid regimes differed, with some studies (24, 28) citing regimes used in other inflammatory conditions in which ILS use is established, such as acute and chronic skin lesions and capsulitis (34), while others based on the number, size and distance of lesions (23), and on the clinical experience of the treating clinician (25, 26). In the ILS group the complete response rates of studies were 91.7% for Methylprednisolone, Triamcinolone (94.1%) and Betamethasone (90.3%). This shows that all three types of steroids have similar efficacy when used intralesionally. In comparison, the studies that used OS regimens, showed an 80% complete response rate in the prednisolone group and 90.1% in the methylprednisolone group (26, 28). The single study that used a combined treatment with both oral and ILS also showed a complete response in 89.5%.

The dosage or the frequency of injection did not show a correlation with the complete response rate. The main determinants of these factors were the severity of the disease.

Similar observations were noted in the complete response time. In the ILS group this ranged from one to six months with a mean of 2.6 months whereas, in the OS group it ranged from one to nine months with a mean of 6.4 months. The oral Prednisolone group also appears to have had a longer mean clinical response time of 6.4 months (21)

Table 5. Comparison of outcomes of each group

Study	Steroid used	Complete response rate	Mean complete response time (months)	Recurrence rate
Group 1 (ILS)				
Alper et al. (22) 2020	Methylprednisolone	25 (89.3%)	NAD	0 (0%)
Toktas and Toprak (27) 2021	Methylprednisolone	6 (100%)	1.2	1 (16.7%)
Ertürk et al. (23) 2022	Triamcinolone acetonide	36 (94.5%)	Large lesions-3 Small lesions-2 (Median) Range: 1-5	0 (0%)
Kim et al. (24) 2016	Triamcinolone	15 (100%)	3.8	0 (0%)
Tang et al. (25) 2020	Triamcinolone	12 (100%)	2 (Median)	0 (0%)
Toktas et al. (26) 2021	Triamcinolone acetonide	34 (91.2%)	NAD	4 (10.8%)
Yildirim et al. (28) 2021	Triamcinolone acetonide	15 (88.2%)	NAD	NAD
Karami et al. (21) 2022	Betamethasone disodium	28 (90.3%)	3.17 Range: 1–6	6 (16.3%)
Group 2 (OS)				
Karami et al. (21) 2022	Prednisolone	24 (80%)	6.37 Range: 6–9	1 (3.3%)
Toktas et al. (26) 2021	Methylprednisolone	29 (90.6%)	2.1 Range: 1–3	15 (48.4%)
Yildirim et al. (28) 2021	Methylprednisolone	17 (89.5%)	1.82 Range: 1–3	NAD
Group 3 (Surgery)				
Ertürk et al. (23) 2022	N/A	48 (100%)	N/A	15 (31.2%)
Tang et al. (25) 2020	N/A	9 (100%)	N/A	0 (0%)
Group 4 (Combined)				
Karami et al. (21) 2022	IL betamethasone + OS prednisolone	34 (89.5%)	4.33 Range: 1–6	5 (13.2%)

NAD: No available data; N/A: Not applicable; OS: Oral steroid; ILS: Intralesional steroid

compared to the studies using Methylprednisolone with response times of 1.8 (28) and 2.1 months (26). The combined group showed a mean complete response time of 4.3 months.

Therefore, the efficacy of ILS use in IGM was comparable to the oral and combined steroid groups.

Comparison of Complications Related to Treatment

The overall complication rate also appears to be lower in the ILS Group (3.8%) compared to the OS (9.9%), surgery (8.3%) and combined treatment (10.5%) groups. Most importantly, complications following ILS were minor, with hematomas, skin atrophy and hyperemia being commonly described. Three patients treated with ILS had skin atrophy, of which two were from groups that did not concurrently use topical steroids. The ILS group avoided systemic side effects of OS use such as weight gain and hirsutism, which were the most widely reported side effects in the OS and combined group. These systemic side effects have significant medical and psychological impacts in the demographic that is affected by IGM.

Post-operative pain is a significant complication of surgical excision, with the study done by Ertürk et al. (23) demonstrating significantly higher pain scores in the surgical group as compared to the ILS group. In addition, the inherent poorer cosmetic outcomes of surgery add to the unfavorable outcomes of that intervention. However, aesthetic outcome has not been described in any of the selected studies. Combined therapies, such as those with MTX have the highest complication rate, with other factors such as problems with compliance making this modality questionable, more so considering the non-inferiority of ILS monotherapy in terms of complete response rates, response times and minimal complications

Comparison of Recurrence

Within the ILS group, the recurrence rate of the single study (21) that used Betamethasone (19.35%) appears to be higher than that of studies that used Methylprednisolone (2.94%) and Triamcinolone (3.36%). Possible causes for this discrepancy could be due to the heterogeneity of dosage and frequency, and further comparative studies would be useful to establish a significant difference.

In comparison the recurrence rates in the ILS Group (6.6%) and Combined Group (13.2%) appear to be lower than in the OS Group (25.8%) and Surgery Group (26.3%). The recurrence rate of oral steroids appears to be similar in other studies focusing on recurrence with OS use, which highlighted patient age, radiological residual disease, and non-compliance as independent risk factors (35, 36). One possible explanation for this discrepancy could be because intralesional steroids achieve persistently high therapeutic levels of steroid concentration at the target site compared to oral steroids alone, resulting in prolonged resolution. The high recurrence rates of surgical intervention are also comparable to other reported studies (37, 38). The higher recurrence rates in surgery have mainly been attributed to residual disease post excision, which can be mitigated with repeated ILS use, which is less invasive.

Study Limitations

A major limitation of the studies included was that the distributions of principal confounders in each group of subjects to be compared were not clearly described. Furthermore, there was also a lack of adequate adjustment for confounding factors in the analyses from which the main findings were drawn. Factors, such as severity of the disease condition, the presence of complications such as abscesses and fistulae (and the additional management of such complications), the use of ultrasound to guide intralesional injections, the exact formulation of intralesional injections (diluents, etc.), the use of other treatment modalities such as MTX and antibiotics, as well as the variability of patients' perception of the efficacy of each modality of treatment and clinical reasoning which led to selection of treatment modalities were not clearly defined. The statistical power of individual studies was also limited as the sample sizes were limited, and the required sample size to detect a significant difference was not calculated in most studies. Other limitations included the lack of randomization and blinding of patients and evaluators.

In conclusion, ILS seem to show a favorable outcome in terms of complete response rate, complete clinical response time and have a lower recurrence rate and complication rate as compared to other intervention strategies and may be considered as first-line therapy in the management of IGM. However, more comparative studies with standardized protocols are necessary to ascertain the optimum type, dosage, and frequency of ILS regimens.

Authorship Contributions: Surgical and Medical Practices: A.W., J.S., B.W., J.F., U.J., A.D.S., K.W.; Concept: A.W., A.D.S., K.W.; Design: A.W., K.L., J.S., B.W., J.F., U.J., A.D.S., K.W.; Data Collection or Processing: A.W., K.L., J.S., B.W., J.F., U.J., A.D.S., K.W.; Analysis or Interpretation: A.W., K.L., B.W., J.F., U.J., A.D.S., K.W.; Literature Search: A.W., J.S., B.W., J.F., U.J., A.D.S., K.W.; Writing: A.W., J.S., U.J., A.D.S., K.W.

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

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

References

1. Benson JR, Dumitru D. Idiopathic granulomatous mastitis: presentation, investigation and management. Future Oncol 2016; 12: 1381-1394. (PMID: 27067146) [Crossref]
2. Agrawal A, Pabolu S. A Rare Case of Idiopathic Granulomatous Mastitis in a Nulliparous Woman with Hyperprolactinemia. Cureus 2019; 11: e4680. (PMID: 31328071) [Crossref]
3. Al Manasra AR, Al-Hurani MF. Granulomatous Mastitis: A Rare Cause of Male Breast Lump. Case Rep Oncol 2016; 9: 516-519. (PMID: 27721777) [Crossref]
4. Kessler E, Wolloch Y. Granulomatous mastitis: a lesion clinically simulating carcinoma. Am J Clin Pathol 1972; 58: 642-646. (PMID: 4674439) [Crossref]
5. Nguyen MH, Molland JG, Kennedy S, Gray TJ, Limaye S. Idiopathic granulomatous mastitis: case series and clinical review. Intern Med J 2021; 51: 1791-1797. (PMID: 34713960) [Crossref]
6. Barreto DS, Sedgwick EL, Nagi CS, Benveniste AP. Granulomatous mastitis: etiology, imaging, pathology, treatment, and clinical findings. Breast Cancer Res Treat 2018; 171: 527-534. (PMID: 29971624) [Crossref]
7. Nikolaev A, Blake CN, Carlson DL. Association between Hyperprolactinemia and Granulomatous Mastitis. Breast J 2016; 22: 224-231. (PMID: 26705962) [Crossref]
8. Troxell ML, Gordon NT, Doggett JS, Ballard M, Vetto JT, Pommier RF, et al. Cystic Neutrophilic Granulomatous Mastitis: Association With Gram-Positive Bacilli and Corynebacterium. Am J Clin Pathol 2016; 145: 635-645. (PMID: 27247368) [Crossref]

9. Ramadan R, Koryem IM, Fayed H. Idiopathic granulomatous mastitis: Risk factors and management. Breast Dis 2022; 41: 413-420. (PMID: 36530069) [Crossref]
10. Baslaim MM, Khayat HA, Al-Amoudi SA. Idiopathic granulomatous mastitis: a heterogeneous disease with variable clinical presentation. World J Surg 2007; 31: 1677-1681. (PMID: 17541683) [Crossref]
11. Freeman CM, Xia BT, Wilson GC, Lewis JD, Khan S, Lee SJ, et al. Idiopathic granulomatous mastitis: A diagnostic and therapeutic challenge. Am J Surg 2017; 214: 701-706. (PMID: 28739122) [Crossref]
12. Dursun M, Yilmaz S, Yahyayev A, Salmaslioglu A, Yavuz E, Igci A, et al. Multimodality imaging features of idiopathic granulomatous mastitis: outcome of 12 years of experience. Radiol Med 2012; 117: 529-538. (PMID: 22020426) [Crossref]
13. Hovanessian Larsen LJ, Peyvandi B, Klipfel N, Grant E, Iyengar G. Granulomatous lobular mastitis: imaging, diagnosis, and treatment. AJR Am J Roentgenol 2009; 193: 574-581. (PMID: 19620458) [Crossref]
14. Alper F, Abbasguliyev H, Özmen S, Yalçin A, Yılmaz Çankaya B, Akçay MN. Clinical, Histopathological, Imaging, and Treatment Perspectives of Inflammatory Granulomatous Mastitis: Review of the Literature. Eurasian J Med 2022; 54(Suppl 1): 172-178. (PMID: 36655464) [Crossref]
15. Davis J, Cocco D, Matz S, Hsu CH, Brown MJ, Lee J, et al. Re-evaluating if observation continues to be the best management of idiopathic granulomatous mastitis. Surgery 2019; 166: 1176-1180. (PMID: 31400951) [Crossref]
16. Basim P, Argun D, Argun F. Risk Factors for Idiopathic Granulomatous Mastitis Recurrence after Patient-Tailored Treatment: Do We Need an Escalating Treatment Algorithm? Breast Care (Basel) 2022; 17: 172-179. (PMID: 35707181) [Crossref]
17. Yuan QQ, Xiao SY, Farouk O, Du YT, Sheybani F, Tan QT, et al. Management of granulomatous lobular mastitis: an international multidisciplinary consensus (2021 edition). Mil Med Res 2022; 9: 20. (PMID: 35473758) [Crossref]
18. Bede K, Valente SA. Idiopathic granulomatous mastitis. Ann Breast Surg 2020; 4: 24. [Crossref]
19. Munot K, Nicholson S, Birkett V. Granulomatous mastitis - A novel method of treatment. EJSO 2012; 38: 461-462. [Crossref]
20. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998; 52: 377-384. (PMID: 9764259) [Crossref]
21. Karami MY, Zangouri V, Habibagahi Z, Tahmasebi S, Ranjbar A, Seyyedy MS, et al. The effectiveness of local steroid injection for the treatment of breast-limited idiopathic granulomatous mastitis: A randomized controlled clinical trial study. 2022. [Crossref]
22. Alper F, Karadeniz E, Güven F, Yılmaz Çankaya B, Özden K, Akçay MN. The evaluation of the efficacy of local steroid administration in idiopathic granulomatous mastitis: The preliminary results. Breast J 2020; 26: 309-311. (PMID: 31495032) [Crossref]
23. Ertürk TF, Çakır Ö, Yaprak Bayrak B, Güneş A, Aydemir S, Utkan NZ. Local steroid treatment: An effective procedure for idiopathic granulomatous mastitis, including complicated cases. J Invest Surg 2022; 35: 745-751. (PMID: 34154493) [Crossref]
24. Kim BS, Koo BY, Eom TI. Usefulness of ultrasound-guided intralesional steroid injection in management of idiopathic granulomatous mastitis. J Surg Ultrasound 2016; 3: 40-45. [Crossref]
25. Tang A, Dominguez DA, Edquilang JK, Green AJ, Khoury AL, Godfrey RS. Granulomatous Mastitis: Comparison of Novel Treatment of Steroid Injection and Current Management. J Surg Res 2020; 254: 300-305. (PMID: 32497924) [Crossref]
26. Toktas O, Konca C, Trabulus Didem C, Soyder A, Koksal H, Karanlik H, et al. A Novel First-Line Treatment Alternative for Noncomplicated Idiopathic Granulomatous Mastitis: Combined İntralesional Steroid İnjection with Topical Steroid Administration. Breast Care (Basel) 2021; 16: 181-187. (PMID: 34012373) [Crossref]
27. Toktas O, Toprak N. Treatment Results of Intralesional Steroid Injection and Topical Steroid Administration in Pregnant Women with Idiopathic Granulomatous Mastitis. Eur J Breast Health 2021; 17: 283-287. (PMID: 34263157) [Crossref]
28. Yildirim E, Kayadibi Y, Bektas S, Ucar N, Oymak A, Er AM, et al. Comparison of the efficiency of systemic therapy and intralesional steroid administration in the treatment of idiopathic granulomatous Mastitis. The novel treatment for Granulomatous Mastitis. Ann Ital Chir 2021; 92: 234-241. (PMID: 34193647) [Crossref]
29. Rice JB, White AG, Scarpati LM, Wan G, Nelson WW. Long-term Systemic Corticosteroid Exposure: A Systematic Literature Review. Clin Ther 2017; 39: 2216-2229. Epub 2017 Oct 19. (PMID: 29055500) [Crossref]
30. Deshmukh NS, Belgaumkar VA, Mhaske CB, Doshi BR. Intralesional drug therapy in dermatology. Indian J Dermatol Venereol Leprol 2017; 83: 127-132. (PMID: 27647355) [Crossref]
31. Savant S. Textbook of dermatosurgery and cosmetology. Indian Journal of Dermatology, Venereology, and Leprology 2005; 71: 304. [Crossref]
32. Hollander A. Intralesional injections of triamcinolone acetonide; a therapy for dermatoses. Antibiotic Med Clin Ther (New York) 1961; 8: 78-83. (PMID: 13715299) [Crossref]
33. Verbov J. The place of intralesional steroid therapy in dermatology. Br J Dermatol 1976; 94(Suppl 12): 51-58. (PMID: 131575) [Crossref]
34. de Jong BA, Dahmen R, Hogeweg JA, Marti RK. Intra-articular triamcinolone acetonide injection in patients with capsulitis of the shoulder: a comparative study of two dose regimens. Clin Rehabil 1998; 12: 211-215. (PMID: 9688036) [Crossref]
35. Çetin K, Sıkar HE, Feratoğlu F, Taşdoğan B, Güllüoğlu BM. Treatment of Granulomatous Mastitis With Steroids: Should the Decision to End the Treatment be Made Radiologically? Eur J Breast Health 2024; 20: 25-30. (PMID: 38187102) [Crossref]
36. Tan QW, Zhang YN, Jia YP, Gou J, Lv Q, Yang XQ. Methylprednisolone for idiopathic granulomatous mastitis: a prospective observational cohort study. Gland Surg 2022; 11: 1538-1545. (PMID: 36221278) [Crossref]
37. Shin YD, Park SS, Song YJ, Son SM, Choi YJ. Is surgical excision necessary for the treatment of Granulomatous lobular mastitis? BMC Womens Health 2017; 17: 49. (PMID: 28738795) [Crossref]
38. Kok KY, Telisinghe PU. Granulomatous mastitis: presentation, treatment and outcome in 43 patients. Surgeon 2010; 8: 197-201. (PMID: 20569938) [Crossref]

Original Article

Eur J Breast Health 2024; 20(4): 241-250
DOI: 10.4274/ejbh.galenos.2024.2024-5-1

The Predictive Role of Mammography, Dynamic Contrast-Enhanced Breast Magnetic Resonance Imaging and Diffusion-Weighted Imaging in Hormone Receptor Status of Pure Ductal Carcinoma *In Situ* Lesions

Almıla Coşkun Bilge[1], Zarife Melda Bulut[2]

[1]Department of Radiology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey
[2]Department of Pathology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey

ABSTRACT

Objective: The aim of this retrospective study was to analyze the predictive capabilities of preoperative mammography, dynamic contrast-enhanced-magnetic resonance imaging (DCE-MRI), and diffusion-weighted imaging (DWI) in determining hormone receptor (HRc) status for pure ductal carcinoma *in situ* (DCIS) lesions.

Materials and Methods: The study included a total of 79 patients who underwent preoperative mammography (MG) and MRI between December 2018 and December 2023 and were subsequently diagnosed with pure DCIS after surgery. The correlation between MG, DCE-MRI, and DWI features and estrogen receptor (ER) and progesterone receptor (PR) status was examined.

Results: Among the lesions, 44 were double HRc-positive (ER and PR-positive), 13 were single HRc-positive (ER-positive and PR-negative or ER-negative and PR-positive) and 22 were double HRc-negative (ER and PR-negative). The presence of symptom (p = 0.029), the presence of comedo necrosis (p = 0.005) and high histological grade (p<0.001) were found to be associated with ER and PR negativity. Amorphous microcalcifications were more commonly observed in the double HRc-negative group, while linear calcifications were more prevalent in both double and single HRc-positive groups (p = 0.020). Non-mass enhancement (NME) with a linear distribution was significantly more common in double HRc-negative lesions (38%), and NME with a segmental distribution in both double (43%) and single (50%) receptor-positive lesions (p = 0.042). Evaluation of DWI findings revealed that a higher lesion-to-normal breast parenchyma apparent diffusion coefficient (ADC) ratio statistically increased the probability of HRc positivity (p = 0.033).

Conclusion: Certain clinicopathological, mammography, and MRI features, along with the lesion-to-normal breast parenchyma ADC ratio, can serve as predictors for HRc status in DCIS lesions.

Keywords: Ductal carcinoma *in situ*; mammography; magnetic resonance imaging; diffusion-weighted MRI; estrogen receptor; progesterone receptor

Cite this article as: Coşkun Bilge A, Bulut ZM. The Predictive Role of Mammography, Dynamic Contrast-Enhanced Breast Magnetic Resonance Imaging and Diffusion-Weighted Imaging in Hormone Receptor Status of Pure Ductal Carcinoma *In Situ* Lesions. Eur J Breast Health. 2024; 20(4): 241-250

Key Points

- Ductal carcinoma *in situ* is a heterogeneous disease in terms of its histopathological features, which is a precursor to invasive breast cancer.
- Evaluation of hormone receptor status is important for preoperative treatment planning.
- The presence of symptoms, the presence of comedo necrosis, histological grade, microcalcification morphology, the distribution pattern of non-mass enhancement, and tumor-to-normal parenchyma apparent diffusion coefficient ratio may be considered valuable in preoperatively predicting hormone receptor status in cases of ductal carcinoma *in situ*.

Introduction

Ductal carcinoma *in situ* (DCIS) is recognized as a precursor to invasive breast cancer, comprising approximately 25-30% of all breast cancers today (1, 2). DCIS is a heterogeneous disease depending on its histopathological and biological features (2, 3). Molecular subtyping primarily relies on the analysis of hormone receptors (HRc), such as estrogen receptor (ER) and progesterone receptor (PR) (2). The few published studies exploring the impact of molecular characteristics on prognosis in DCIS indicate that HRc-negative lesions tend to be associated with local recurrence (4, 5). The assessment of prognostic factors holds significance in guiding treatment management. Based on these evaluations, appropriate treatment strategies for DCIS

Corresponding Author:
Almıla Coşkun Bilge; almilacoskun@gmail.com

Received: 04.05.2024
Accepted: 15.06.2024
Available Online Date: 26.09.2024

are determined, encompassing surgical options (mastectomy/lumpectomy), radiation therapy, and adjuvant hormone therapy (1, 2, 5).

Core needle biopsies (CNBs) are regarded as the gold standard for preoperative breast tumor diagnosis. However, under sampling during CNBs and the highly heterogeneous internal pattern of DCIS lesions can contribute to pathologically uncertain interpretations (6). Radiological imaging methods play a crucial role in characterizing the entire tumor. Mammography (MG) is the primary imaging modality for diagnosing DCIS, with calcification being the dominant reported feature (7). ER-positive DCIS commonly present as fine pleomorphic and fine-linear branching calcifications (6). Additionally, the literature defines other findings, such as architectural distortions, masses, and focal densities (8). Dynamic contrast-enhanced-magnetic resonance imaging (DCE-MRI) provides high sensitivity for breast lesions (7). Preoperative MRI can provide essential data to reveal the extent of disease and assist in surgical management planning for DCIS cases (9). DCIS lesions typically manifest as clumped nonmass enhancement (NME) in a segmental or linear distribution, with plateau or washout kinetic curves (7, 10). While DCE-MRI reveals the morphology and vascularization of lesions, diffusion-weighted imaging (DWI) provides insights into tissue cellularity and the integrity of cell membranes. Quantitative evaluation of DWI features involves obtaining apparent diffusion coefficient (ADC) values from DWI images. DCIS lesions generally exhibit lower ADC values compared to normal breast tissue and benign lesions (11).

The potential heterogeneous distribution of antigens within DCIS lesions raises concerns about the accuracy of HRc profiling based on samples obtained via CNB, as they may not fully represent the complete tumor tissue (12). A non-invasive, biopsy-complementary method capable of assessing the entire lesion is thus important for predicting the presence of ER and PR in DCIS. Integrating preoperative MG and DWI into DCE-MRI protocols holds promise for differentiating the HRc status of DCIS lesions (13). However, it is noteworthy that there are fewer reports evaluating DCE-MRI and DWI findings according to HRc status in pure DCIS lesions compared to investigations focusing on MG findings (14, 15).

The aim of this study was to assess whether findings from MG, DCE-MRI and DWI can predict the HRc status in cases of pure DCIS.

Materials and Methods

This retrospective study received approval from the Non-Interventional Clinical Research Ethics Committee of Health Sciences University Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Health Education Application and Research Center (no.: 2023-12/123, date: 14.12.2023), and informed consent was obtained from each participant.

Patients

Data from 489 patients histopathologically diagnosed with pure DCIS following breast-conserving surgery or mastectomy at our institute between December 2018 and December 2023 were retrospectively accessed from the electronic medical record archive. From this cohort, 124 patients with preoperative MG, DCE-MRI, and DWI images were identified in our radiology image archive. Exclusion criteria were applied to ensure the study's integrity, resulting in the exclusion of 45 patients. Reasons for exclusion included receiving neoadjuvant chemotherapy or endocrine therapy (n = 35), having DWI images unsuitable for measuring the ADC value due to artifacts (n = 6), or having lesions smaller than 5 mm where region of interest (ROI) measurements were not feasible (n = 4). The final participant count in the study stood at 79. Clinical characteristics such as age, symptoms, risk factors, and histopathological features of the lesions were meticulously extracted from the patients' medical records.

Mammography Technique

MG was conducted using a digital MG system (LORAD, Hologic Company, Selenia Mammography System, Danbury, USA). Craniocaudal and mediolateral oblique views were acquired as part of the routine MG imaging process. For a more detailed assessment of low-density microcalcifications with ambiguous morphology and distribution in standard MG, a magnification view was employed, using a magnification factor of 1.8. A spot compression view, employing a compression paddle, was conducted to discern focal asymmetric densities or mass lesions visible in routine MG, distinguishing them from superpositions with surrounding tissue and enhancing visualization of lesion boundaries. The resulting images were presented on a pair of high-resolution 5-megapixel 21-inch LCD monitors (Coronis MDMG-5121, Barco, Belgium).

Mammography Findings

A radiologist with 13 years of experience in breast imaging conducted retrospective review of the MG images without access to the clinical information or pathological outcomes of the cases. Lesions were categorized into four groups based on mammographic findings: occult, mass, calcifications, and mass with microcalcifications. The morphological features of calcifications and masses, as well as the distribution of calcifications, were meticulously assessed using the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) lexicon (American College of Radiology, 2013) (16). The shape of the mass was described as either oval/round or irregular, with its margin defined as either circumscribed or indistinct/spiculated. Calcifications were morphologically classified as amorphous, coarse heterogeneous, fine pleomorphic, and fine linear/branching. The distribution of calcifications was subgrouped as regional, grouped, linear, and segmental. Following the comprehensive evaluation of the MG views, an MG-BI-RADS category was assigned to each case.

MRI Technique

MRI examinations were conducted using a 1.5-Tesla MR scanner (SignaHDx; GE Healthcare, Wisconsin, USA) with the patient positioned prone and with a dedicated breast coil. The MRI sequences and corresponding image parameters were as follows: Axial short tau inversion recovery [repetition time/echo time (TR/TE): 6500/45, inversion time: 150 ms, field of view (FOV): 320 mm, matrix: 416 × 224, number of excitations (NEX): 1, and slice thickness (ST): 5 mm]; axial T1-weighted (T1W) (TR/TE: 400/8.8, FOV: 320 mm, matrix: 448 × 224, NEX: 1, and ST: 5 mm); dynamic axial fat-saturated T1W (before and after contrast injection) (TR/TE: 4/1.5, flip angle: 10°, FOV: 320 mm, matrix: 350 × 350, NEX: 1, and ST: 2.8 mm); and echo-planar imaging-based DWI (TR/TE: 1000/83, FOV: 320 mm, matrix: 192 × 192, NEX: 4, ST: 5 mm, with b-values of 0 and 800 s/mm^2). Each patient underwent one pre-contrast scan, and dynamic series comprising five post-contrast scans following intravenous administration of a contrast agent injection (0.1 mmol/kg gadobutrol/gadopentetate dimeglumine) at a dose of 0.1 mmol per kilogram

of body weight, followed by a 20 mL saline flush. Subtraction, multiplanar reconstruction, and maximum-intensity projection images were automatically generated on a dedicated workstation. Applying ROI drawing, ADC values were obtained. The ROI area was adjusted based on the lesion size, with a mean ROI size of 54 mm² (range, 35–110 mm²).

MRI Findings

The preoperative breast MRI images for all cases underwent retrospective review on a workstation by a radiologist with 13 years of experience in breast imaging. The radiologist conducted the analysis in a blinded manner, without access to clinical information or pathologic outcomes. MRI findings for each lesion were systematically analyzed following the BI-RADS MRI lexicon, encompassing morphological and enhancement features (16).

Lesion morphology was differentiated into mass and NME. For mass lesions, shape features were characterized as oval/round or irregular, while margin features were defined as circumscribed or not circumscribed (irregular and spiculated), in accordance with the BI-RADS MRI lexicon. NME lesion distributions were classified as focal, linear, segmental, or regional.

Internal enhancement patterns were categorized as homogeneous, heterogeneous, or rim for mass lesions, and as homogeneous, heterogeneous, clumped, or clustered ring for NME lesions. A time-intensity curve was automatically generated by placing the cursor on the most intensely and suspiciously enhanced areas of the lesions on postcontrast images. The obtained kinetic curves were scrutinized, and the contrast enhancement patterns were determined for both the initial phase (slow, medium, or rapid) and the delayed phase (persistent, plateau, or washout).

ADC value measurements were conducted in areas corresponding to the lesions identified in DCE-MRI images on ADC maps resulting from the processing of DWI images. Oval or round ROIs were drawn on ADC maps for both the lesion and normal breast parenchyma (in the same quadrant as the lesion in the contralateral breast or in the ipsilateral breast in cases with contralateral mastectomy/lumpectomy) (Figure 1). Minimum ADC values were computed for the lesion and maximum ADC values for the normal tissue. The measured minimum ADC values of the lesions and the ratio of lesion ADC to normal parenchyma ADC were documented.

Pathological Evaluation

Lumpectomy or mastectomy materials underwent evaluation by a pathologist with 22 years of expertise in breast pathology. The assessment included determining tumor tissues through ER and PR staining, evaluating tumor viability, and ensuring the presence of a sufficient tumor area. Under light microscopy, nuclear ER and PR expression in areas of DCIS were examined in tissue samples. Tumors with ≥10% nuclear staining were deemed receptor-positive. DCIS lesions were further categorized into three groups based on their immunohistochemical profile: Double hormone receptor-positive (ER-positive, PR-positive), single hormone receptor-positive (ER-positive, PR-negative or ER-negative, PR-positive), and double hormone receptor-negative (ER-negative, PR-negative). Furthermore, DCIS was stratified into low-, intermediate-, or high-grade. In addition, and following the College of American Pathologists protocol, the presence of comedo necrosis was defined. The pathology reports, encompassing the aforementioned information, were retrospectively obtained from the electronic medical archive of our hospital.

Statistical Analysis

Statistical analyses were executed using IBM SPSS software, version 20.0 (IBM Corporation, Armonk, NY, USA). Clinicopathological and radiological data were stratified based on the hormone receptor status of DCIS lesions, delineated as double positive (ER-positive/PR-positive), single positive (ER-positive/PR-negative or ER-negative/PR-positive), and double negative (ER-negative/PR-negative). Descriptive statistics, including mean, standard deviation, median, minimum,

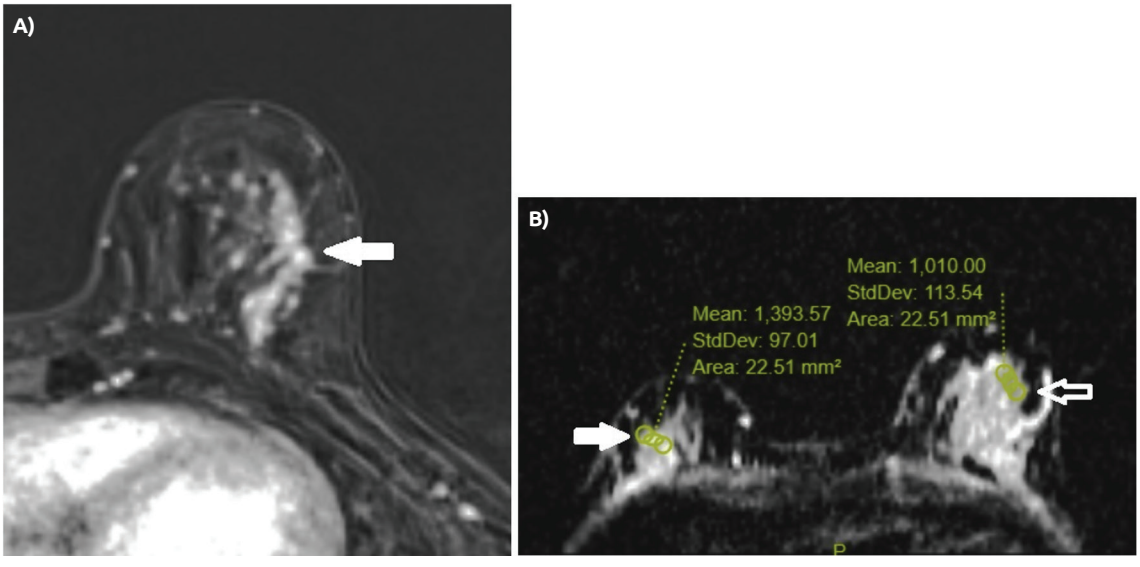

Figure 1. A 54-year-old woman with high-grade pure DCIS containing foci of comedo necrosis. Immunohistochemical analysis established that ER was positive and PR was negative. **A)** Axial postcontrast subtraction image showed a heterogeneous nonmass enhancement with segmental distribution in the left breast (arrow). **B)** ADC measurements were made from the lesion (empty arrow) and from the same quadrant as the lesion in the contralateral breast parenchyma (arrow) in the ADC map. The minimum lesion ADC value was 1010×10^{-6}mm²/second, the maximum normal breast parenchyma ADC value was 1393×10^{-6}mm²/second, and the lesion- normal breast parenchyma ADC ratio was 0.72

DCIS: Ductal carcinoma in situ; ER: Estrogen receptor; PR: Progesterone receptor; ADC: Apparent diffusion coefficient

maximum, and percentages, were produced. For categorical variables, such as clinicopathological data, MG, and DCE-MRI findings, the chi-square test or Fisher exact test, if necessary, was employed to assess their association with the hormone receptor status of DCIS lesions. Normality analyses were conducted for continuous variables, including patient age, lesion size, lesion ADC value, and lesion-to-normal breast parenchyma ADC ratio, using the Kolmogorov-Smirnov goodness-of-fit test and Shapiro-Wilk test. To evaluate significant differences in continuous dependent variables between groups, the Kruskal-Wallis H test was used for lesion size, ADC value, and lesion-to-normal breast parenchyma ADC ratio, while One-Way ANOVA was employed for the patient age variable. A *p*-value less than 0.05 was considered statistically significant. The threshold value of the lesion/normal breast parenchyma ADC ratio was determined using receiver operating characteristic (ROC) analysis. The optimal cut-off for the lesion/normal parenchyma ADC ratio was determined with reference to the Youden index.

Results

Clinicopathological Features

In the histopathological assessment of 79 DCIS lesions, 44 were found to be ER and PR-positive, 13 were ER-positive and PR-negative or ER-negative and PR-positive, and 22 were ER and PR-negative. The mean age of the study participants was 50.96±12.14 years (range 24 - 79 years). Upon comparing the groups, no significant relationship was identified between the HRc status and patient age (p = 0.150). Patients over the age of 50 were distributed in the double HRc-positive, single HRc-positive, and double HRc-negative groups at rates of 45%, 46%, and 63%, respectively (p = 0.356). The rate of symptomatic patients in the ER and PR-negative group was 63%, which was significant. Specifically, the rate of symptomatic patients was 63% in the ER and PR-negative group, 29% in the ER and PR-positive group, and 38% in the single HRc-positive group (p = 0.029). No significant difference was observed between the groups regarding the presence of breast cancer risk factors (p = 0.556) (Table 1). The median histopathologically confirmed size of DCIS lesions was 25 mm (range 5 - 85 mm). The lesion size, even when subgrouped by 20 mm, did not exhibit statistically significant differences in intergroup comparisons (p = 0.556). Comedo necrosis was identified in 77% of ER and PR-negative lesions, 76% of single HRc-positive lesions, and 40% of ER and PR-positive lesions, showing a significant relationship with the HRc status of the DCIS lesions (p = 0.005). Moreover, DCIS with a high histological grade was predominantly found in the ER and PR-negative group (95%), followed by the single receptor-positive group (46%), and the ER and PR-positive group (43%) (p<0.001).

Mammography Findings

In each group, DCIS lesions predominantly manifested as microcalcifications on MG, with rates of 38% for the double HRc-positive group, 69% for the single HRc-positive group, and 31% for the double HRc-negative group (p = 0.348). The intergroup distribution of shape and margin characteristics of lesions in mass morphology is detailed in Table 2, revealing no statistically significant differences (p = 0.494, p = 1.000, respectively). Examining the distribution of microcalcification morphology between groups, fine pleomorphic microcalcifications were detected in 50% and 60% of the double and single HRc-positive groups, respectively, while amorphous microcalcifications were observed in 50% of the HRc-negative group (p = 0.020) (Figure 2). However, no significant correlation was found between the distribution patterns of microcalcifications and the HRc status of the lesions (p = 0.856). MG BI-RADS category 4C was identified in 31% of double HRc-positive and HRc-negative lesions and 38% of single HRc-positive lesions, with no significant difference found between the groups (p = 0.998).

DCE-MRI Findings

In MRIs, the predominant lesion morphological types in the double HRc-positive, single HRc-positive, and double HRc-negative groups were NME in 84%, 92%, and 81%, respectively (p = 0.831). A single mass lesion was identified in the single HRc-positive group with an irregular shape and margin. For both ER and PR-positive and -negative groups, the dominant mass shape was round/ovoid (71% and 75%, respectively), while the predominant margin feature was irregular/spiculated (71% and 100%, respectively). There were no significant differences in the shape and margin characteristics of mass lesions between the groups (p = 0.463 and p = 0.576, respectively). While NME with a segmental distribution was commonly observed in both double (43%) and single (50%) HRc-positive lesions, NME with a linear distribution was more frequent in HRc-negative lesions (38%) (Figure 3). Statistically significant differences were found in the distribution of NME lesions between the groups p = 0.042. Regarding the internal enhancement pattern of NME, the clumped pattern was predominant in both double HRc-positive (51%) and negative (33%) lesions, while the heterogeneous enhancement pattern prevailed in single HRc-positive lesions (50%) (p = 0.186). The distribution of

Table 1. Clinicopathological features of the cases according to hormone receptor subgroups

	ER/PR positive (n) (%)	Single positive (n) (%)	ER/PR negative (n) (%)	*p*-value
Age (grouped)				
≤50 years	24 (54.5)	7 (53.8)	8 (36.4)	0.356
>50 years	20 (45.5)	6 (46.2)	14 (63.6)	
Symptom				
No	31 (70.5)	8 (61.5)	8 (36.4)	0.029
Yes	13 (29.5)	5 (38.5)	14 (63.6)	
Risk factors				
No	33 (75)	11 (84.6)	15 (68.2)	0.556
Yes	11 (25)	2 (15.4)	7 (31.8)	
Size (grouped)				
≤20 mm	20 (45.5)	4 (30.8)	9 (40.9)	0.638
>20 mm	24 (54.5)	9 (69.2)	13 (59.1)	
Comedo necrosis				
No	26 (59.1)	3 (23.1)	5 (22.7)	0.005
Yes	18 (40.9)	10 (76.9)	17 (77.3)	
Histological grade				
Low	6 (13.6)	1 (7.6)	0 (0)	
Intermediate	19 (43.2)	6 (46.2)	1 (4.6)	<0.001
High	19 (43.2)	6 (46.2)	21 (95.4)	

ER: Estrogen receptor; PR: Progesterone receptor

Table 2. Mammographic findings of the lesions according to hormone receptor subgroups

	ER/PR positive (n) (%)	Single positive (n) (%)	ER/PR negative (n) (%)	*p*-value
Mammography findings				
Occult	9 (20.5)	0 (0)	6 (27.3)	0.348
Mass	11 (25)	3 (23.1)	6 (27.3)	
Microcalcification	17 (38.6)	9 (69.3)	7 (31.8)	
Microcalcification+mass	7 (15.9)	1 (7.6)	3 (13.6)	
Mass shape				
Round/ovoid	4 (22.2)	0 (0)	3 (33.3)	0.494
Lobular/irregular	14 (77.8)	4 (100)	6 (66.7)	
Mass margin				
Smooth circumscribed	1 (5.6)	0 (0)	1 (11.1)	1.000
Indistinct/spiculated	17 (94.4)	4 (100)	8 (88.9)	
Microcalcification morphology				
Amorphous	8 (33.4)	1 (10)	5 (50)	0.020
Course heterogeneous	2 (8.3)	2 (20)	2 (20)	
Fine pleomorphic	12 (50)	6 (60)	0 (0)	
Fine linear/fine linear branching	2 (8.3)	1 (10)	3 (30)	
Microcalcification distribution				
Regional	1 (4.2)	1 (10)	0 (0)	0.856
Grouped	12 (50)	4 (40)	4 (40)	
Linear	0 (0)	0 (0)	0 (0)	
Segmental	11 (45.8)	5 (50)	6 (60)	
MG-BI-RADS				
Category 4A	5 (14.3)	2 (15.4)	2 (12.6)	0.998
Category 4B	11 (31.4)	3 (23.1)	5 (31.2)	
Category 4C	11 (31.4)	5 (38.4)	5 (31.2)	
Category 5	8 (22.9)	3 (23.1)	4 (25)	

ER: Estrogen receptor; PR: Progesterone receptor; MG: Mammography; BI-RADS: Breast imaging reporting and data system

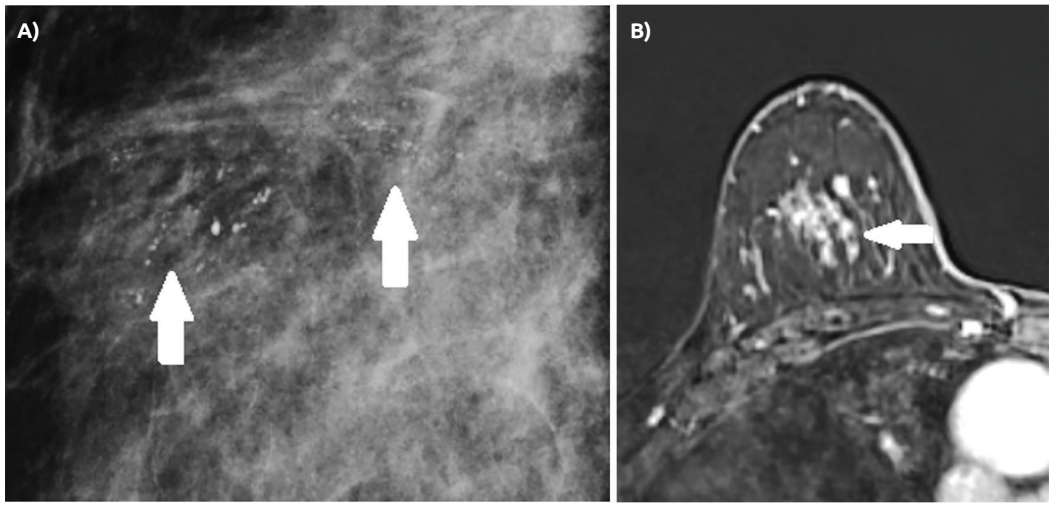

Figure 2. A 45-year-old woman with high-grade pure DCIS containing foci of comedo necrosis. Immunohistochemical analysis established that ER and PR were negative. **A.** A magnification view in the CC mammogram projection showed grouped amorphous calcifications (arrows). **B.** Axial postcontrast subtraction MRI image showed a clumped nonmass enhancement with focal distribution in the right breast (arrow)

DCIS: Ductal carcinoma in situ; ER: Estrogen receptor; PR: Progesterone receptor; CC: Craniocaudal; MRI: Magnetic resonance imaging

initial and delayed phase kinetic patterns is detailed in Table 3 and did not exhibit significant differences between the three groups (p = 0.400 and p = 0.105, respectively). The lesions were categorized as MRI BI-RADS 4 in 72% of the double HRc-positive group, 61% of the single HRc-positive group, and 81% of the double HRc-negative group. No statistically significant difference was found between receptor subgroups in terms of the MRI BI-RADS category (p = 0.412).

ADC Values

The median ADC value of DCIS lesions was $1323\times10^{-6}mm^2$/sec in ER and PR-positive group, $1196\times10^{-6}mm^2$/sec in single HRc-positive group and $1245\times10^{-6}mm^2$/sec in the ER and PR-negative group. However, no significant relationship was observed between the lesion ADC value and HRc status (p = 0.388).

Table 3. DCE-MRI findings of the lesions according to hormone receptor subgroups

	ER/PR positive (n) (%)	Single positive (n) (%)	ER/PR negative (n) (%)	*p*-value
MRI findings				
Mass	7 (15.9)	1 (7.6)	4 (18.2)	0.831
NME	37 (84.1)	12 (92.4)	18 (81.8)	
Mass shape				
Round/ovoid	5 (71.4)	0 (0)	3 (75)	0.463
Lobular/irregular	2 (28.6)	1 (100)	1 (25)	
Mass margin				
Circumscribed	2 (28.6)	0 (0)	0 (0)	0.576
Irregular/spiculated	5 (71.4)	1 (100)	4 (100)	
Mass internal enhancement pattern				
Homogeneous	3 (42.8)	0 (0)	0 (0)	
Heterogeneous	4 (57.2)	1 (100)	4 (100)	0.427
Rim	0 (0)	0 (0)	0 (0)	
NME distribution				
Focal	12 (32.4)	5 (41.7)	3 (16.7)	
Linear	2 (5.4)	0 (0)	7 (38.9)	
Segmental	16 (43.3)	6 (50)	6 (33.3)	0.042
Regional	7 (18.9)	1 (8.3)	2 (11.1)	
Diffuse	0 (0)	0 (0)	0 (0)	
NME enhancement pattern				
Homogeneous	3 (8.1)	0 (0)	5 (27.8)	
Heterogeneous	8 (21.6)	6 (50)	4 (22.2)	0.186
Clumped	19 (51.4)	5 (41.7)	6 (33.3)	
Clustered ring	7 (18.9)	1 (8.3)	3 (16.7)	
Initial phase kinetic pattern				
Slow	14 (31.9)	3 (23.1)	6 (27.3)	
Medium	13 (29.5)	7 (53.8)	5 (22.7)	0.400
Rapid	17 (38.6)	3 (23.1)	11 (50)	
Delayed phase kinetic pattern				
Persistent	8 (18.2)	6 (46.2)	6 (27.2)	
Plateau	26 (59.1)	3 (23.1)	8 (36.4)	0.105
Washout	10 (22.7)	4 (30.7)	8 (36.4)	
MRI-BI-RADS				
Category 4	32 (72.7)	8 (61.5)	18 (81.8)	0.412
Category 5	12 (27.3)	5 (38.5)	4 (18.2)	

ER: Estrogen receptor; PR: Progesterone receptor; NME: Nonmass enhancement; DCE-MRI: Dynamic contrast-enhanced magnetic resonance imaging; BI-RADS: Breast imaging reporting and data system

The lesion-to-normal breast parenchyma ADC ratio showed notable variation across HRc status, being highest in double HRc-positive lesions (0.89) and lowest in double HRc-negative lesions (0.76). The ADC ratio demonstrated a significant association with the HRc status of DCIS lesions (p = 0.033) (Table 4). In the ROC curve analysis, the highest AUC [0.66 (0.53–0.78)] was obtained using an ADC ratio of 0.80 as the threshold, with corresponding sensitivity and specificity values of 66% and 65%, respectively (Figure 4).

Discussion and Conclusion

The current study assessed the predictive role of clinicopathological, MG, DCE-MRI features, and ADC values in determining the HRc status of pure DCIS lesions. Of the DCIS lesions in our study, 55% were histopathologically diagnosed as ER and PR-positive. This rate is slightly lower than that reported in a study with a larger patient population, where the rate of double HRc-positive cases was 68% (5). Hwang et al. (5) noted that younger mean patient ages were associated with ER and PR positivity compared to other DCIS subtypes. In our investigation, the relatively lower rate of HRc-positive cases was considered to be associated with the older mean patient age in the study. Furthermore, the present study revealed that age was not a significant factor in predicting the HRc status of DCIS.

While DCIS is often asymptomatic, it can present with clinical symptoms such as a palpable mass, nipple discharge, or Paget's disease (8, 17). Consistent with the literature, symptomatic DCIS cases were observed more frequently in the HRc-negative group in our study (17, 18). Rapid growth and progression leading to symptoms are associated with a poorer prognosis for DCIS (17, 18). HRc-positive DCIS lesions are known to have a tendency to increase slowly in size (4). In keeping with this, the smallest mean size among the three groups was observed in the HRc-positive group in our study. Therefore, it was not surprising that ER and PR-positive lesions were mostly asymptomatic. Comedo necrosis and high histological grade are considered aggressive histopathologic factors for DCIS lesions (19, 20). In the present study, these poor prognostic factors were observed at a higher rate in ER and PR-negative cases, consistent with previous studies in the literature (19, 21). The mentioned histopathologic features and the HRc status of the DCIS lesions showed a significant correlation.

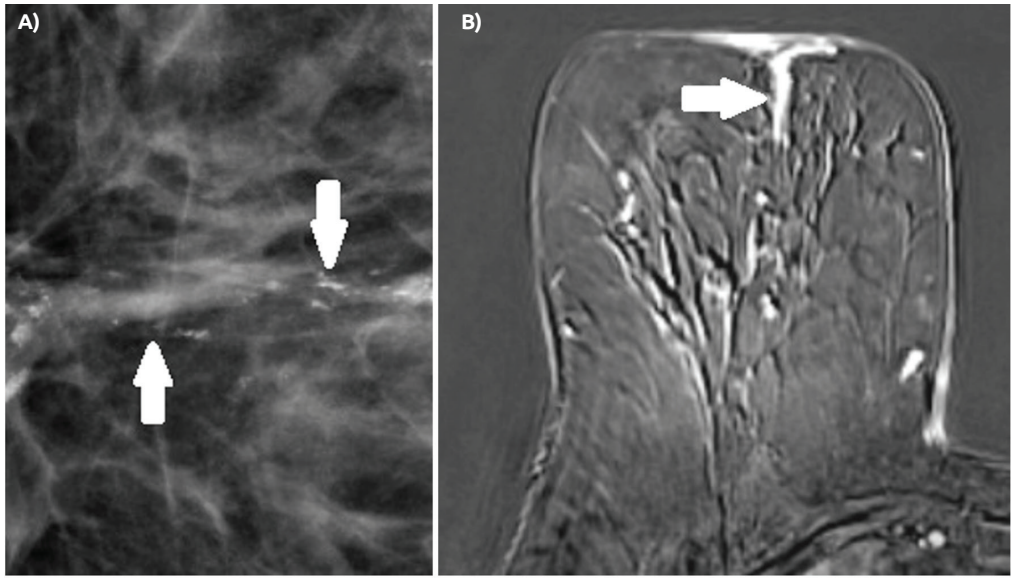

Figure 3. A 55-year-old woman with high-grade pure DCIS without comedo necrosis. Immunohistochemical analysis established that ER and PR were negative. **A.** A magnification view in the CC mammogram projection showed grouped fine pleomorphic and fine linear calcifications (arrows). **B.** Axial postcontrast subtraction MRI image showed a homogeneous nonmass enhancement with linear distribution in the right breast (arrow)

DCIS: Ductal carcinoma in situ; ER: Estrogen receptor; PR: Progesterone receptor; CC: Craniocaudal; MRI: Magnetic resonance imaging

Table 4. Comparison of patient's age, lesion size, lesion ADC value, and lesion-to-normal breast parenchyma ADC ratio according to hormone receptor subgroups

	ER/PR positive (n) (%)	Single positive (n) (%)	ER/PR negative (n) (%)	*p*-value
Patient age (year) (mean ± SD)	49.59±10.07	47.31±9.34	55.86±15.89	0.150
Lesion size (mm) (median) (min-max)	23.5 (7–70)	36 (9–85)	35 (5–68)	0.240
Lesion ADC value ($10^{-6}mm^2$/sec) (median) (min-max)	1323 (1015–1699)	1196 (1005–1599)	1245 (976–1895)	0.388
Lesion/normal breast parenchyma ADC ratio (median) (min-max)	0.89 (0.63–0.99)	0.82 (0.66–0.95)	0.76 (0.66–0.98)	0.033

ER: Estrogen receptor; PR: Progesterone receptor; ADC: Apparent diffusion coefficient; SD: Standard deviation; Min: Minimum; Max: Maximum

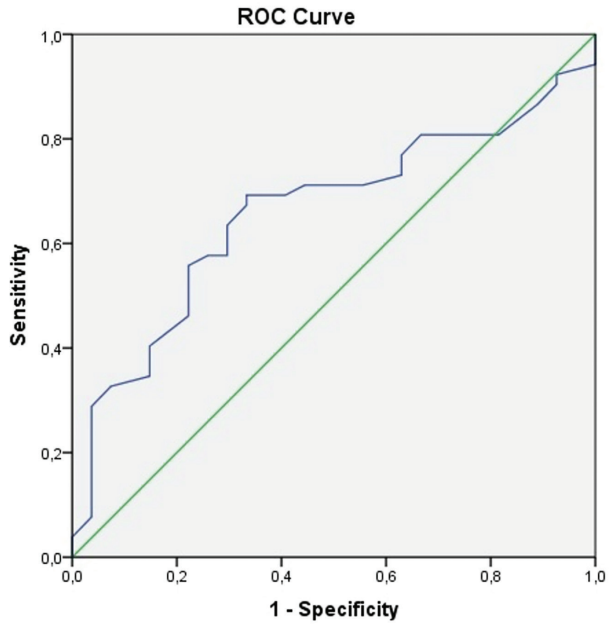

Figure 4. Graph shows ROC curve for differentiating double HRc positive DCIS from other HRc status of DCIS on the basis of lesion-to-normal breast parenchyma ADC ratio. The area under the ROC curve was 0.66 (95% CI: 0.53–0.78)

ROC: Receiver operating characteristic; HRc: Hormone receptor; DCIS: Ductal carcinoma in situ; ADC: Apparent diffusion coefficient CI: Confidence interval

Microcalcification is the predominant and prevalent manifestation of DCIS lesions in MG (2, 22, 23). The pathophysiology underlying calcification formation involves the concentration of mucin secretions within the duct/lobular acini or the calcification of endoluminal necrotic material, which comprises cell debris and excretions (24). The diversity in calcification morphologies and distributions stems from the variance in developmental mechanisms (2, 22). In the present study, a significant correlation was identified between calcification morphology and HRc status. In line with earlier published findings, the current investigation revealed that DCIS lesions with double and single positive-HRc were more frequently associated with fine pleomorphic calcifications, while ER and PR-negative DCIS lesions were more likely to exhibit amorphous calcifications (2, 19, 25). Moreover, across all three groups, the predominant distribution of calcifications was segmental and grouped, with no significant differences observed between the groups. This result is in keeping with those reported by Kim et al. (19). Of note, in previous studies that established a significant relationship between calcification distribution and receptor status, the number of cases in the receptor-negative group was notably low, potentially impacting the reliability of their results (2, 25).

In MG, the identification of DCIS lesions often hinges on the presence of suspicious calcifications. However, lesions devoid of calcification can also be encountered, rendering MG insufficient for DCIS diagnosis in such instances (26). Previous studies have reported the incidence of mammographically occult DCIS to range from 6% to 23% (8). Our study corroborates this trend, revealing a 19% rate, aligning with the existing literature. Given its high sensitivity for pure DCIS (77–96%), MRI proves valuable in accurately delineating the extent of the disease (6, 7). In MRI, the increased permeability of vascular and basement membranes in DCIS results in the accumulation of gadolinium contrast agent in ducts and terminal lobules, leading to the most common presentation of DCIS on MRI as NME with a segmental or linear distribution (6, 14, 26). Our study concurs with these results, identifying NME as the most prevalent morphology across all three groups, in line with the literature. Moreover, HRc-positive lesions, both double and single, predominantly exhibited a segmental distribution, while HRc-negative lesions displayed a more frequent linear distribution on DCE-MRI. A notable correlation was established between the distribution of NME and the HRc status of the lesions. While previous studies have described typical enhancement patterns of DCIS lesions as clumped or heterogeneous, our investigation revealed a predominantly clumped pattern in both HRc-positive and -negative groups, with a heterogeneous pattern observed in the single HRc-positive group (7, 27). Notably, no association was identified between the enhancement pattern of the lesions and the groups. Kinetic data derived from DCE-MRI, when evaluated alongside other imaging data, can aid in the differential diagnosis of breast lesions. The kinetic curve of lesions, influenced by factors such as angiogenesis, leaky vasculature, cellularity, and changes in extracellular interstitial space, may vary for each lesion due to the contribution of these pathophysiological factors at different rates (15, 28).

Numerous prior studies have consistently identified the rapid initial phase with washout delayed phase enhancement as the prevailing kinetic pattern for DCIS (7, 27, 28). Our study showed a predominant display of a rapid initial enhancement with a plateau kinetic curve in DCIS lesions, echoing the results reported by Kim et al. (15). In a study by Bharti et al. (29), heightened microvessel proliferation was notably more common in ER-negative tumors. Building upon this insight, significant intergroup differences in the kinetic characteristics of DCIS lesions were initially anticipated in our investigation. Contrary to this expectation, our study revealed no discernible differences in the kinetic features of pure DCIS lesions based on HRc status.

DWI is an MRI technique that does not require a contrast agent, relying on the assessment of the random Brownian motion of water molecules within tissue (11, 13). The impedance of water molecular diffusion is influenced by the degree of tissue cellularity and the permeability of cell membranes (30). ADC serves as a quantifiable measure to evaluate this diffusion. ER and PR, and intranuclear receptors that impact DNA and participate in cell proliferation, may also influence the expression of aquaporins responsible for transporting water across cell membranes, thereby regulating tissue water diffusion (13). In the present study, ADC values for pure DCIS lesions were measured, with the aim of assessing their potential in discriminating HRc status. Rahbar et al. revealed similar ADC values for high nuclear grade and non-high nuclear grade DCIS lesions (11). Iima et al. (30) proposed that DCIS lesions with ADC values below 1.3 were likely to be low-grade. In addition, Rocknsharifi et al. (13) found lower ADC values in PR-negative breast cancer lesions, including DCIS and invasive tumors. While our results indicated a relatively lower ADC value in single HRc-positive pure DCIS lesions compared to other groups, our investigation ultimately found no significant difference in ADC values between the groups. To the best of our knowledge, no studies comparable to the current investigation have explored the correlation between ADC values and HRc status in DCIS. The variation in hormonal levels influences the water content in the interstitial area of breast tissue, as well as the proliferative activity of luminal epithelial cells and mitotic activity in breast lobules. Postmenopausal changes lead to a significant reduction in tissue water

content and cell proliferation. Consequently, ADC values in the breast parenchyma may vary significantly among individual patients (31, 32). Moreover, previous studies have established a correlation between decreased ADC in breast tumors and increased cellularity compared to normal fibroglandular tissue (10, 11). Recognizing this, it was posited that a more accurate assessment could be derived from the ratio of ADC values for DCIS lesions to normal breast parenchyma. Our study found that the lesion-to-normal breast parenchyma ADC ratio was associated with the HRc status of DCIS lesions. Thus it is suggested that the likelihood of double HRc positivity increased at values above 0.8, identified as the threshold. This observation aligned with our discovery that the ER and PR-positive group exhibited the highest ADC values.

Several limitations were inherent in our study. Firstly, the retrospective nature and the single-center design with a limited sample size may impact the generalizability of our results. Future research endeavors should focus on multicenter prospective investigations involving larger patient cohorts to validate our results and uncover potential new associations. Secondly, our inclusion criteria, which involved cases undergoing preoperative MG and MRI, may introduce selection bias. Cases with dense artifacts in DWI images and very small lesions (<5 mm) were excluded, potentially limiting the representativeness of our results for all DCIS lesions. Thirdly, the heterogeneous internal structure of DCIS lesions posed challenges in standardizing kinetic evaluation and ADC measurements. Fourthly, in our study HER-2 expression, which is indicated in the literature as a prognostic factor for recurrence of DCIS lesions and response to radiotherapy, was not investigated (33, 34). The reason for this is that HER-2 expression is not routinely evaluated in DCIS at our center. Finally, the retrospective interpretation of MG and MRI images by a single radiologist may introduce variability, given the morphological intralesional heterogeneity of DCIS. Different outcomes might have been observed if multiple radiologists had evaluated the images.

In conclusion, our study identified clinicopathological features such as the presence of symptoms and comedo necrosis, and high histological grade, along with amorphous microcalcifications and the linear distribution pattern of NME, as potential indicators for HRc-negativity in DCIS. Furthermore, a lesion-to-normal parenchyma ADC ratio threshold of 0.80 was established as predictive for ER and PR-positive DCIS lesions. To the best of our knowledge, no study in the literature has investigated MRI features based on HRc status in pure DCIS lesions, making our study a potential guide in this unexplored area.

Ethics Committee Approval: This retrospective study received approval from the Non-Interventional Clinical Research Ethics Committee of Health Sciences University Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Health Education Application and Research Center (no.: 2023-12/123, date: 14.12.2023).

Informed Consent: Informed consent was obtained from each participant.

Authorship Contributions

Surgical and Medical Practices: A.C.B., Z.M.B.; Concept: A.C.B.; Design: A.C.B., Z.M.B.; Data Collection and/or Processing: A.C.B., Z.M.B.; Analysis and/or Interpretation: A.C.B.; Literature Search: A.C.B.; Writing: A.C.B.

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

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

References

1. Villanueva H, Grimm S, Dhamne S, Rajapakshe K, Visbal A, Davis CM, et al. The Emerging Roles of Steroid Hormone Receptors in Ductal Carcinoma in Situ (DCIS) of the Breast. J Mammary Gland Biol Neoplasia. 2018; 23: 237-248. (PMID: 30338425) [Crossref]
2. Avdan Aslan A, Gültekin S, Esendağli Yilmaz G, Kurukahvecioğlu O. Is There Any Association Between Mammographic Features of Microcalcifications and Breast Cancer Subtypes in Ductal Carcinoma In Situ? Acad Radiol. 2021; 28: 963-968. (PMID: 32620528) [Crossref]
3. Stanciu-Pop C, Nollevaux MC, Berlière M, Duhoux FP, Fellah L, Galant C, et al. Morphological intratumor heterogeneity in ductal carcinoma in situ of the breast. Virchows Arch. 2021; 479: 33-43. (PMID: 33502600) [Crossref]
4. Tay THC, Ng WY, Ong KW, Wong CY, Tan BKT, Yong WS, et al. Impact of hormonal status on ductal carcinoma in situ of the breast: Outcome and prognostic factors. Breast J. 2020; 26: 937-945. (PMID: 31876337) [Crossref]
5. Hwang KT, Suh YJ, Park CH, Lee YJ, Kim JY, Jung JH, et al. Hormone Receptor Subtype in Ductal Carcinoma in Situ: Prognostic and Predictive Roles of the Progesterone Receptor. Oncologist. 2021; 26: e1939-e1950. (PMID: 34402131) [Crossref]
6. Grimm LJ, Rahbar H, Abdelmalak M, Hall AH, Ryser MD. Ductal Carcinoma in Situ: State-of-the-Art Review. Radiology. 2022; 302: 246-255. (PMID: 34931856) [Crossref]
7. Jansen SA, Newstead GM, Abe H, Shimauchi A, Schmidt RA, Karczmar GS. Pure ductal carcinoma in situ: kinetic and morphologic MR characteristics compared with mammographic appearance and nuclear grade. Radiology. 2007; 245: 684-691. (PMID: 18024450) [Crossref]
8. Shin HJ, Kim HH, Kim SM, Kwon GY, Gong G, Cho OK. Screening-detected and symptomatic ductal carcinoma in situ: differences in the sonographic and pathologic features. AJR Am J Roentgenol. 2008; 190: 516-525. (PMID: 18212241) [Crossref]
9. Benveniste AP, Ortiz-Perez T, Ebuoma LO, Sepulveda KA, Severs FJ, Roark A, et al. Is breast magnetic resonance imaging (MRI) useful for diagnosis of additional sites of disease in patients recently diagnosed with pure ductal carcinoma in situ (DCIS)? Eur J Radiol. 2017; 96: 74-79. (PMID: 29103479) [Crossref]
10. Greenwood HI, Wilmes LJ, Kelil T, Joe BN. Role of Breast MRI in the Evaluation and Detection of DCIS: Opportunities and Challenges. J Magn Reson Imaging. 2020; 52: 697-709. (PMID: 31746088) [Crossref]
11. Rahbar H, Partridge SC, Eby PR, Demartini WB, Gutierrez RL, Peacock S, et al. Characterization of ductal carcinoma in situ on diffusion weighted breast MRI. Eur Radiol. 2011; 21: 2011-2019. (PMID: 21562806) [Crossref]
12. Arnedos M, Nerurkar A, Osin P, A'Hern R, Smith IE, Dowsett M. Discordance between core needle biopsy (CNB) and excisional biopsy (EB) for estrogen receptor (ER), progesterone receptor (PgR) and HER2 status in early breast cancer (EBC). Ann Oncol. 2009; 20: 1948-1952. (PMID: 19570962) [Crossref]
13. Roknsharifi S, Fishman MDC, Agarwal MD, Brook A, Kharbanda V, Dialani V. The role of diffusion weighted imaging as supplement to dynamic contrast enhanced breast MRI: Can it help predict malignancy,

histologic grade and recurrence? Acad Radiol. 2019; 26: 923-929. (PMID: 30293819) [Crossref]

14. Liu H, Peng W. MRI morphological classification of ductal carcinoma in situ (DCIS) correlating with different biological behavior. Eur J Radiol. 2012; 81: 214-217. (PMID: 21296513) [Crossref]
15. Kim JA, Son EJ, Youk JH, Kim EK, Kim MJ, Kwak JY, et al. MRI findings of pure ductal carcinoma in situ: kinetic characteristics compared according to lesion type and histopathologic factors. AJR Am J Roentgenol. 2011; 196: 1450-1456. (PMID: 21606313) [Crossref]
16. Morris EA, Comstock CE, Lee CH. ACR BI-RADS®. In: ACR BI-RADS® Atlas, Breast imaging reporting and data system. Reston, VA: American College of Radiology. 2013:56-71. [Crossref]
17. Barnes NL, Dimopoulos N, Williams KE, Howe M, Bundred NJ. The frequency of presentation and clinico-pathological characteristics of symptomatic versus screen detected ductal carcinoma in situ of the breast. Eur J Surg Oncol. 2014; 40: 249-254. (PMID: 24433818) [Crossref]
18. Koh VC, Lim JC, Thike AA, Cheok PY, Thu MM, Tan VK, et al. Characteristics and behaviour of screen-detected ductal carcinoma in situ of the breast: comparison with symptomatic patients. Breast Cancer Res Treat. 2015; 152: 293-304. (PMID: 26077641) [Crossref]
19. Kim MY, Kim HS, Choi N, Yang JH, Yoo YB, Park KS. Screening mammography-detected ductal carcinoma in situ: mammographic features based on breast cancer subtypes. Clin Imaging. 2015; 39: 983-986. (PMID: 26259866) [Crossref]
20. Moon HJ, Kim EK, Kim MJ, Yoon JH, Park VY. Comparison of Clinical and Pathologic Characteristics of Ductal Carcinoma in Situ Detected on Mammography versus Ultrasound Only in Asymptomatic Patients. Ultrasound Med Biol. 2019; 45: 68-77. (PMID: 30322671) [Crossref]
21. Barnes NL, Boland GP, Davenport A, Knox WF, Bundred NJ. Relationship between hormone receptor status and tumour size, grade and comedo necrosis in ductal carcinoma in situ. Br J Surg. 2005; 92: 429-434. (PMID: 15736216) [Crossref]
22. Tang X, Yamashita T, Hara M, Knox WF, Bundred NJ. Histopathological characteristics of breast ductal carcinoma in situ and association with imaging findings. Breast Cancer. 2016; 23: 491-498. (PMID: 15736216) [Crossref]
23. Kim JH, Ko ES, Kim DY, Han H, Sohn JH, Choe DH. Noncalcified ductal carcinoma in situ: imaging and histologic findings in 36 tumors. J Ultrasound Med. 2009; 28: 903-910. (PMID: 19546332) [Crossref]
24. Henrot P, Leroux A, Barlier C, Génin P. Breast microcalcifications: the lesions in anatomical pathology. Diagn Interv Imaging. 2014; 95: 141-152. (PMID: 24525087) [Crossref]
25. Bae MS, Moon WK, Chang JM, Cho N, Park SY, Won JK, et al. Mammographic features of calcifications in DCIS: correlation with oestrogen receptor and human epidermal growth factor receptor 2 status. Eur Radiol. 2013; 23: 2072-2078. (PMID: 23512196) [Crossref]
26. Scott-Moncrieff A, Sullivan ME, Mendelson EB, Wang L. MR imaging appearance of noncalcified and calcified DCIS. Breast J. 2018; 24: 343-349. (PMID: 29139591) [Crossref]
27. Chan S, Chen JH, Agrawal G, Lin M, Mehta RS, Carpenter PM, et al. Characterization of Pure Ductal Carcinoma In Situ on Dynamic Contrast-Enhanced MR Imaging: Do Nonhigh Grade and High Grade Show Different Imaging Features? J Oncol. 2010; 2010: 431341. (PMID: 20885929) [Crossref]
28. Chen ST, Covelli J, Okamoto S, Daniel BL, DeMartini WB, Ikeda DM. Clumped vs non-clumped internal enhancement patterns in linear non-mass enhancement on breast MRI. Br J Radiol. 2021; 94: 20201166. (PMID: 33332980) [Crossref]
29. Bharti JN, Rani P, Kamal V, Agarwal PN. Angiogenesis in Breast Cancer and its Correlation with Estrogen, Progesterone Receptors and other Prognostic Factors. J Clin Diagn Res. 2015; 9: EC05-EC07. (PMID: 25737993) [Crossref]
30. Iima M, Le Bihan D, Okumura R, Okada T, Fujimoto K, Kanao S, et al. Apparent diffusion coefficient as an MR imaging biomarker of low-risk ductal carcinoma in situ: a pilot study. Radiology. 2011; 260: 364-372. (PMID: 21633054) [Crossref]
31. Mori N, Mugikura S, Takasawa C, Miyashita M, Shimauchi A, Ota H, et al. Peritumoral apparent diffusion coefficients for prediction of lymphovascular invasion in clinically node-negative invasive breast cancer. Eur Radiol. 2016; 26: 331-339. (PMID: 26024846) [Crossref]
32. Ramakrishnan R, Khan SA, Badve S. Morphological changes in breast tissue with menstrual cycle. Mod Pathol. 2002; 15: 1348-1356. (PMID: 12481017) [Crossref]
33. Yang L, Shen M, Qiu Y, Tang T, Bu H. Molecular subtyping reveals uniqueness of prognosis in breast ductal carcinoma in situ patients with lumpectomy. Breast. 2022; 64: 1-6. (PMID: 35462343) [Crossref]
34. Thorat MA, Levey PM, Jones JL, Pinder SE, Bundred NJ, Fentiman IS, et al. Prognostic and Predictive Value of HER2 Expression in Ductal Carcinoma In Situ: Results from the UK/ANZ DCIS Randomized Trial. Clin Cancer Res. 2021; 27: 5317-5324. (PMID: 34380636) [Crossref]

Original Article

Eur J Breast Health 2024; 20(4): 251-257
DOI: 10.4274/ejbh.galenos.2024.2024-5-7

Reliability of L-Dex Scores for Assessment of Unilateral Breast Cancer-Related Lymphedema

Leigh C. Ward[1,2], Katrina Gaitatzis[1], Belinda Thompson[1], Vincent Singh Paramanandam[1], Louise A. Koelmeyer[1]

[1]Australian Lymphoedema Education, Research and Treatment Centre, Department of Health Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia
[2]School of Chemistry and Molecular Biosciences, The University of Queensland, St. Lucia, Brisbane, Australia

ABSTRACT

Objective: Breast cancer-related lymphedema (BCRL) is a common complication of breast cancer treatment that may result in swelling of the affected arm due to compromised lymphatic function. Implementing a screening program and early intervention for BCRL are important for effective management. Bioimpedance spectroscopy (BIS) is a commonly used tool for assessing BCRL. This study aimed to compare different normative ranges for BIS L-Dex scores in the detection of BCRL.

Materials and Methods: Data from 158 women with clinically ascribed and indocyanine green confirmed BCRL were analysed. BIS measurements were obtained using an ImpediMed standing device, and L-Dex scores were calculated using published normative ranges for healthy individuals. Statistical analysis was performed to compare the concordance between different reference ranges in classifying individuals with lymphedema.

Results: The study found that L-Dex scores calculated using different normative ranges were highly correlated and essentially interchangeable in detecting BCRL. Approximately 90% of participants exceeded the L-Dex threshold for lymphedema, with minimal discrepancies between reference ranges. False negative rates were observed in some participants, likely due to early-stage BCRL with minimal lymph accumulation.

Conclusion: The findings suggest that BIS L-Dex scores are a valid indicator of BCRL, regardless of specific normative ranges used. Detection rates of clinically confirmed BCRL were consistent across different reference ranges, with minimal discrepancies. BIS remains a valuable tool for early detection and monitoring of BCRL. Future research should focus on longitudinal assessments and use of change in L-Dex scores for lymphedema monitoring and progression.

Keywords: Lymphedema; bioimpedance spectroscopy; impedance; L-Dex

Cite this article as: Ward LC, Gaitatzis K, Thompson B, Paramanandam VS, Koelmeyer LA. Reliability of L-Dex Scores for Assessment of Unilateral Breast Cancer-Related Lymphedema. Eur J Breast Health. 2024; 20(4): 251-257

Key Points

- Breast cancer-related lymphedema (BCRL) is a common complication of breast cancer treatment that can result in swelling of the affected arm.
- Implementing a screening program and early intervention for BCRL are crucial for effective management.
- L-Dex scores calculated using different normative ranges were highly correlated and essentially interchangeable in detecting BCRL.
- Future research should focus on longitudinal assessments and use of change in L-Dex scores for lymphedema monitoring and progression.

Introduction

Secondary lymphedema is a chronic condition of lymphatic dysfunction characterised by swelling of a body region due to accumulation of excess lymph fluid through compromised lymph transport (1). The aetiology of lymphedema is varied but is well recognised as an adverse sequala of breast cancer and its treatment; this is breast cancer-related lymphedema (BCRL) (2). Estimates of BCRL incidence vary but range from 3 to 65% with presentation occurring most commonly within two years of surgery (3, 4). The precise mechanisms for development of BCRL are uncertain but is likely due to direct damage to the lymphatics through either surgery or radiation treatment rather than damage due to the presence of a tumour *per se* (2-5).

Increasingly, it is recognised that the recommended standard of care for those undergoing breast cancer treatment is a prospective surveillance and early intervention model (6-9) with lymphedema treatment being most effective when commenced at the earliest opportunity (10). Definitive diagnosis of BCRL is by comprehensive clinical evaluation with objective assessment of lymphatic function by an imaging technique, such as indocyanine green (ICG) lymphography (11) or lymphoscintigraphy (12). In practice, however, initial recognition of

Corresponding Author:
Katrina Gaitatzis; katrina.gaitatzis@mq.edu.au

Received: 29.05.2024
Accepted: 29.06.2024
Available Online Date: 26.09.2024

BCRL is frequently self-assessment of symptoms by the individual or simple visual observation of arm swelling (13). Furthermore, since imaging techniques such as ICG lymphography are frequently only available in tertiary referral settings, objective assessment of BCRL is routinely undertaken by measurement of limb swelling. Although various techniques are available, the most commonly used are simple volumetric measurement of the at-risk limb or assessment of extracellular water (ECW) volume, of which lymph is a principal component, by bioimpedance spectroscopy (BIS) (14). Both of these methods are recommended in best practice guidelines and position statements, e.g., National Comprehensive Cancer Network, USA (15) and the Australasian Lymphology Association (https://www.lymphoedema.org.au/public/7/files/Position%20Statements/ALA%20Position%20Statement_Early%20Detection%20of%20BCRL.pdf).

Although widely used and recommended, neither volumetric assessment nor BIS measure lymphatic dysfunction or lymph accumulation directly. In volumetric assessment, the excess size of the at-risk limb in unilateral BCRL is determined relative to the contralateral limb in either absolute (mL) or relative (%) terms, ideally as volume increase relative to a pre-surgery or pre-treatment baseline measurement where available (16, 17). Volume excess or change in volume of 5 or 10% are commonly used as indicative of BCRL (18, 19). In contrast, BIS provides an indirect index of lymph accumulation. BIS measures the electrical impedance of the arm, which is inversely but quantitatively related to the volume of ECW, including lymph (20). Like volumetric measurements, the low frequency impedance (typically resistance at zero current frequency, R0) of the at-risk limb is compared to that of the contralateral unaffected limb but as a ratio ($R0_{unaffected}$: $R0_{at\text{-}risk}$) rather than as an absolute or percentage difference. Unlike volumetric measurements, impedance ratios typically compared normative values for the impedance ratio observed in a healthy non-BCRL population with the mean control value plus either two (2SD) or three (3SD) standard deviations being used as thresholds indicative of presumptive lymphedema (20). Since impedance ratios are not immediately intuitively understandable, it has become common practice to convert ratios to a linear scale, an L-Dex score, where 2SD and 3SD thresholds correspond to L-Dex scores of 6.5 and 10 respectively (20, 21). Consequently, the utility of L-Dex scores for the early detection and monitoring of BCRL is dependent upon the L-Dex thresholds that are reliant upon using appropriate normative standards. An additional concern is that protocols for BIS assessment have changed since its initial introduction in 2001 (22) with the advent of new BIS devices and a move from measurements made in the supine position to those made when standing (23).

The current study compared BIS L-Dex normative ranges determined with different impedance devices and measurement protocols using published data. The concordance between ranges in classifying individuals with lymphedema was assessed in a cohort of women with ICG lymphography-confirmed BCRL.

Materials and Methods

Participants - BCRL

Data for 158 women with clinically ascribed BCRL and confirmed by ICG lymphography were drawn from a database maintained by the Australian Lymphoedema Education, Research and Treatment Program at Macquarie University. All women had consented to data, collected as part of routine clinical practice, being used for research purposes approved by Macquarie University Ethics Committee (approval number: 52020613914268, date: 27.02.2020) abiding by the Helsinki Declaration governing human experimentation. Clinical evaluations were conducted by experienced lymphedema therapists with BIS measurements obtained by trained research assistants within a single session described previously (24). Presence of BCRL was confirmed by ICG lymphography (11), the arm on the side of cancer treatment was deemed as "affected".

Exclusion criteria were minimal: Participants were required to be female, aged over 18 years, not fitted with an implantable device, e.g., a pacemaker or were pregnant (self-ascribed) as these are contraindications for BIS measurements or had a health condition or were receiving medication that affected body water status which would confound BIS measurements.

Participants With BCRL-Measurements

Measurement procedures have been described in detail elsewhere (24). Briefly, height and weight were measured to 0.1 cm and 0.1 kg resolution using a calibrated wall mounted stadiometer and electronic scale, respectively. Whole arm impedance was measured with an ImpediMed SOZO BIS device (ImpediMed Ltd., Brisbane, Australia) with the participant in standing posture in accordance with manufacturer's recommendations as described previously (23). BIS data was stored in a cloud-based database maintained by the SOZO manufacturer.

Participants-Healthy Non-BCRL Normative Data Ranges

A literature search (using Medline-PubMed) was undertaken to find publications in which either impedance ratios or L-Dex scores had been determined for healthy control populations. Six publications were identified, and details are presented in Table 1 (22, 24-28). Details of participants and measurement procedures in these studies can be found in the relevant publications.

Data Analysis

BIS For Participants With BCRL

BIS data for each arm of all participants were retrieved from the SOZO cloud-based database to provide estimates of resistance at zero frequency (R0) for each arm as described previously (20, 29). R0 ratios were calculated for each participant in the conventional manner as R0_unaffected arm: R0_affected arm. The L-Dex scores were calculated using each of the published normative ranges according to whether the affected limb was dominant or non-dominant.

Statistical Analysis

Impedance data are presented as means ± SD and range. Normal distributions for the published normative range mean and SD were calculated using the normal distribution spreadsheet template provided by Vertex 42 (https://www.vertex42.com/ExcelArticles/mc/NormalDistribution-Excel.html) and distributions compared using the Z statistic. Statistical significance of differences between 2SD L-Dex 6.5 scores calculated using the different normative ranges was determined using a two-factor (range and dominance) repeated measures analysis of variance (ANOVA) (Sigmastat v3.5, Systat software, Chicago, USA). Spearman-rank correlations between L-Dex scores for BCRL participants were calculated using the correlation matrix module of NCCS version 2022 (NCSS LLC, Kaysville, USA). Descriptive statistics and distribution plots of L-Dex scores by reference range were prepared using MedCalc Statistical Software v 22.023 (MedCalc Software Ltd, Ostend, Belgium).

Results

Characteristics of Participants

Characteristics of the BCRL participants are presented in Table 2. The majority of participants with BCRL were overweight (75.3%) according to WHO criteria of body mass index (BMI) >25 kg/m^2 with 39.8% having a BMI >30 kg/m^2. Mean R0 of the affected arm was, on average, 18.4% smaller than that of the unaffected arm reflecting the larger volume of the affected limb. Mean R0 ratio (1.27) was notably larger than the mean values seen in healthy control individuals irrespective of reference population (1.011 to 1.037, Table 1).

Impedance Ratio Normative Ranges

Published reference ranges for impedance ratios and the 2SD and 3SD thresholds, equivalent to L-Dex 6.5 and 10 units respectively, are presented in Table 1. The normal distribution curves are presented in Figure 1. Distributions were overlapping and not significantly different, although not identical, reflecting not only different populations but also devices and measurement protocols. Most studies measured impedance at zero frequency (R0), although Ridner et al. (27) obtained measurements at an unspecified but <30 kHz frequency, while Jung et al. (28) obtained measurements at both 1 and 5 kHz and provided reference values for each.

L-Dex Scores of Participants With BCRL

The relative distributions of L-Dex scores calculated using each of the reference ranges are presented in Figure 2. Values between ranges were highly correlated (Table 3) but were not in absolute agreement. Two-factor ANOVA found no significant overall difference in mean L-Dex score between the different reference ranges although pair-wise comparison showed significant differences (p<0.0001) between all paired comparisons except for the two ranges provided from the same study by Jung et al. (28). Although absolute magnitude of L-Dex values varied with dominance of the affected arm according to dominance-defined normative ranges (Table 1), this was irrespective of the reference range used.

Table 1. Published impedance ratio thresholds for detection of BCRL

Publication	Population	Device	Protocol	Number	Dominant at-risk				Non-dominant at-risk			
					Mean	SD	Mean + 2SD	Mean + 3SD	Mean	SD	Mean + 2SD	Mean + 3SD
Cornish et al. (22)	Caucasian Australia	BIS ImpediMed SFB3	Supine lead electrodes 40-cm segment proximal to wrist	60	1.037	0.034	1.102	1.139	0.964	0.034	1.032	1.066
Ridner et al. (27)	Predominantly Caucasian USA	SFBIA (<30 kHz) ImpediMed XCA	Seated lead electrodes Whole arm (wrist to axilla)	32	1.024	0.040	1.104	1.144	0.986	0.027	1.040	1.060
Ward et al. (25)	Caucasian/ Chinese Australia & New Zealand	BIS ImpediMed SFB3 & SFB7	Supine lead electrodes Whole arm (wrist to axilla)	172	1.014	0.040	1.094	1.134	0.986	0.040	1.066	1.106
Wang et al. (26)	Chinese China	BIS ImpediMed SFB7	Supine lead electrodes Whole arm (wrist to axilla)	391	1.018	0.045	1.108	1.153	0.984	0.044	1.072	1.116
Jung et al. (28)	Korean Korea	MFBIA (1 & 5 kHz) InBody 3.0	Standing plate whole arm (wrist to axilla)	643	[a]1.013	0.030	1.073	1.103	0.998	0.029	1.056	1.085
					[b]1.011	0.029	1.069	1.098	0.990	0.028	1.046	1.074
Ward et al. (24)	Predominantly Caucasian Australia	ImpediMed SOZO & SFB3/7	Standing plate electrodes whole arm (wrist to axilla)	267	1.033	0.041	1.114	1.156	0.972	0.041	1.055	1.097
Weighted average				1565	1.017	0.034	1.085	1.119	0.988	0.034	1.056	1.091

Owing to the larger difference in sample sizes, mean values were calculated weighted according to sample size

BCRL: Breast cancer related lymphedema; BIS: Bioimpedance spectroscopy; MFBIA: Multi-frequence bioimpedance analysis; SD: Standard deviation; [a]: R at 1 kHz; [b]: R at 5 kHz

Table 2. Participant characteristics

Characteristic	BCRL
Number	158
Dominance (right: left)	151:7
At risk (dominant: non-dominant)	76:82
Years since lymphedema diagnosis	4.5±6.1
MDACC ICG stage (number)	
0	1 (0.6%)
1	20 (12.7%)
2	79 (50%)
3	45 (28.5%)
4	13 (8.2%)
Age (years)	57.5±11.8 (32.0 to 82.0)
Height (cm)	163.1±6.6 (144.0 to 178.0)
Weight (kg)	77.4±15.3 (46.2 to 149.8)
Body mass index (kg/m^2)	29.1±5.6 (18.7 to 50.3)
R0 unaffected arm (ohm)	359±43[a] (269 to 488)
R0 affected arm (ohm)	292±63.3[b] (147 to 462)
R0 ratio (unaffected: affected)	1.270±0.254 (0.922 to 2.226)

Data presented as mean ± SD (range)
BCRL: Breast cancer related lymphedema; ICG: Indocyanine green; MDACC: MD Anderson Cancer Center; cm: centimetre; kg: kilogram; m: meter

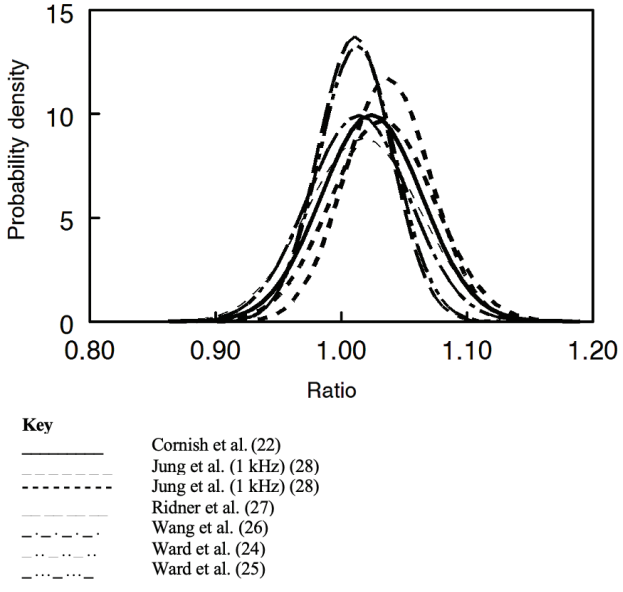

Figure 1. Normal distribution of published R0 ratios

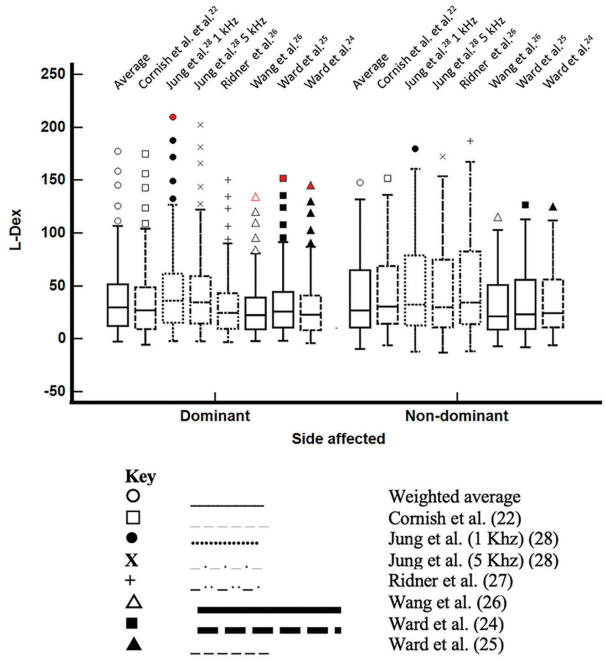

Figure 2. Distributions of L-Dex scores by published reference range

Detection of BCRL by L-Dex Score

An L-Dex score of 6.5 is widely used as a threshold presumptive of the presence of BCRL (30). Although all participants with BCRL on the present study had clinically and ICG lymphography-confirmed lymphedema, 14 (8.9%) provided L-Dex scores <6.5, a consistent finding across all reference ranges (Table 4). A further 3 participants (1.9%) had L-Dex scores ≥6.5 but were negative indicating that the unaffected arm was larger than the affected arm. One hundred and forty-one (89.2%) participants were found to exceed the L-Dex 6.5 threshold by at least one reference range, with 123 (77.8%) of these exceeding this threshold according to all reference range criteria. For the 18 participants in which there were non-concordant L-Dex scores (Table 5), no one reference range was consistently discrepant. The Wang et al. (26) reference range was the only one to be consistent in scoring these participants under the threshold.

Discussion and Conclusion

The present study has demonstrated that the different published reference ranges to establish L-Dex thresholds are highly comparable and essentially interchangeable. This is important since there is no universal consensus on precise measurement procedures or devices to be adopted when BIS is used to assess lymphedema. The detection rate of clinically confirmed lymphedema was approximately 90% irrespective of measurement procedure, with this dropping to 78% where there was 100% agreement between ranges. This lower value is typical of detection rates observed within studies that adopt a single specified reference range (20). Where discrepant results were observed between ranges, the magnitude of L-Dex scores were only just in excess of the 6.5 threshold value. This suggests that in these particular participants, lymphedema may have been at an early or sub-clinical stage where marked lymph accumulation had yet to occur. It is also noteworthy that L-Dex scores fluctuate daily and that a value above a threshold cut-off should not be considered absolutely definitive of the presence of lymphedema, and trends over time are important considerations (27).

Table 3. Correlation matrix for L-Dex scores according to published normative range

Range	Cornish	Ridner	Ward a	Wang	Jung a	Jung b	Ward b	Weighted average
Cornish et al. (22)	1	0.9928	1.0000	0.9996	0.996	0.9781	0.9993	0.9998
Ridner et al. (27)		1	0.9925	0.9951	0.9993	0.9903	0.9888	0.9915
Ward et al. (25)			1	0.9995	0.9957	0.9779	0.9994	0.9998
Wang et al. (26)				1	0.9976	0.982	0.9983	0.9993
Jung et al. (28) (1 kHz)					1	0.9886	0.9928	0.9949
Jung et al. (28) (5 kHz)						1	0.9745	0.9777
Ward et al. (24)							1	0.9997
Weighted average								1

Owing to the larger difference in sample sizes mean values were calculated weighted according to sample size

Table 4. Concordance between reference ranges for detection of lymphedema by L-Dex score ≥6.5

Threshold	Ranges concordant	Participant number (%)
L-Dex <6.5		14 (8.9%)
L-Dex ≥-6.5		3 (1.9%)
	All	141
	6	1
	5	0
L-Dex ≥6.5	4	3
	3	4
	2	7
	1	3

Although not a primary aim of the study, it was found that 17 participants (10.8%) had L-Dex scores negative for lymphedema. This false negative rate is consistent with that observed in other studies (31), but lower than that observed in others (32). A small false negative rate is expected since the thresholds indicative of the presence of lymphedema are defined statistically according to the normal distribution; a 2SD threshold (L-Dex 6.5) means that approximately 5% of a population fall outside a mean + 2SD range. The false negative rate observed here is approximately two-fold greater. It is likely that participants in the early stages of lymphedema have minimal lymph accumulation although ICG lymphography indicates a degree of lymphatic dysfunction. The participants in the present study who provided negative L-Dex (<6.5) were MD Anderson Cancer Center (MDACC) ICG stage 0 (at-risk) (1 participant), 1 (9 participants) or 2 (7 participants) and relatively recently diagnosed, most within two years and a maximum of six years post-lymphedema diagnosis. Three participants presented with L-Dex scores indicating that the unaffected limb was larger, albeit slightly, than the affected limb. The reasons for this are unclear. One was MDACC ICG stage 1 and two were stage 2. All participants had well-managed BCRL, and none were within the obese range where excess adiposity increases ECW. A review of medical records showed two had no obvious confounding characteristics, however one participant had metal in the affected arm from a previous injury which would potentially impact the calculated L-Dex score.

The study has a number of limitations. BIS is used to assess all presentations of lymphedema, unilateral and bilateral, in both arms and legs. The present findings are only appropriate to BIS when used for assessment of unilateral BCRL. Bilateral lymphedema poses difficulty in assessment since there is no contralateral limb for normalization of impedance. L-Dex scores are alternatively calculated, for example, as the ratio of leg to arm impedance values for bilateral lymphedema of the legs (33-36). Few normative ranges for such assessments have been published for comparative analysis. A further limitation is that this analysis is restricted to single L-Dex assessments. It has not considered the preferred use of change in L-Dex scores as an index of lymphedema or when used to monitor progression or response to treatment. This is, however, not considered a major problem since L-Dex scores are calculated in an identical manner using the same reference ranges for determination of threshold values. Three reference ranges considered [Ridner et al. (27) and Jung et al. (28)] were determined using resistance measured at a low frequency but not zero, the optimal frequency for measurement of ECW. The rate change in resistance with frequency however has a low-rate constant (21). York et al. (37) showed that correlation between R0 and resistance measured at frequencies up to 30 kHz ranged from 0.998 to 0.992 while limits of agreement analysis showed that bias was limited to 1.3% at 30 kHz. The generally high agreement found between these studies and those using conventional R0 are consistent with these observations. Finally, L-Dex scores using a 6.5 threshold only were considered. The original BIS protocol used a 3SD threshold. Subsequent research has found that this was too conservative and that a more liberal cut-off of 2SD provided better sensitivity and specificity. Since a change from 2SD to 3SD is a constant scaling effect, this will not affect comparison between reference ranges as considered here; the magnitude of the L-Dex score will be different and the detection rate will be decreased but relativity between ranges will be unaffected.

In conclusion, the current study has confirmed that L-Dex scores are a robust indicator associated with the presence of BCRL. Impedance measurements are reliable for this purpose irrespective of measurement protocol and across different devices. The results also indicate that, assuming electronic accuracy, transferring or upgrading from one device to another will have minimal effect on the value of impedance technology for BCRL detection or monitoring. While this study has affirmed the use of BIS for assessment of BCRL, it should be

Table 5. Lack of agreement between reference ranges for detection of lymphedema by L-Dex score >6.5

	Reference range						
Participant	**Cornish et al. (22)**	**Ward et al. (25)**	**Wang et al. (26)**	**Ward et al. (24)**	**Ridner et al. (27)**	**Jung et al. (28) (1 kHz)**	**Jung et al. (28) (5 kHz)**
A	1.8	4.4	3.4	2.0	3.1	6.0	**6.6**
B	2.0	4.6	3.6	2.1	3.3	6.3	**6.8**
C	**6.7**	3.0	2.9	4.6	4.4	2.0	3.5
D	2.3	4.8	3.9	2.4	3.6	**6.6**	**7.2**
E	3.5	5.9	4.8	3.4	4.6	**8.0**	**8.6**
F	2.4	4.9	3.9	2.5	3.6	**6.7**	**7.3**
G	3.4	5.8	4.7	3.3	4.5	**7.9**	**8.5**
H	2.8	5.3	4.2	2.8	4.0	**7.2**	**7.8**
I	**9.0**	4.9	4.7	**6.5**	**7.3**	4.7	6.3
J	**8.9**	4.8	4.6	6.4	**7.2**	4.6	6.2
K	4.3	**6.5**	5.3	4.0	5.3	**8.9**	**9.5**
L	5.6	**7.6**	6.3	5.1	6.4	**10.3**	**11.0**
M	5.2	**7.3**	6.1	4.8	6.1	**9.9**	**10.6**
N	**9.1**	5.0	4.7	**6.5**	**7.3**	4.8	6.4
O	**9.4**	5.2	5.0	**6.8**	**7.7**	5.1	**6.7**
P	**10.1**	5.9	5.6	**7.4**	**8.7**	6.0	**7.7**
Q	**9.7**	5.5	5.2	**7.0**	**8.1**	5.5	**7.1**
R	**10.9**	**6.5**	6.1	**8.1**	**9.6**	**6.9**	**8.6**

Data presented as L-Dex scores, scores ≥6.5 highlighted in bold

emphasised that BIS is but one technique in the armoury of tools available to a lymphoedema therapist. It is incumbent upon the clinician to be familiar with the relative advantages and disadvantages of each, practicality of use and to use these as an adjunct to their clinical expertise (38).

Acknowledgements

We wish to thank the ALERT research and clinic staff for their assistance with data collection and the participants who have consented to the storage and analysis of their data.

Ethics Committee Approval: The study approved by Macquarie University Ethics Committee (reference number: 52020613914268, date: 27.02.2020).

Informed Consent: All women had consented to data routinely collected data analysed for research purposes.

Authorship Contributions

Concept: L.C.W.; Design: L.C.W.; Data Collection and/or Processing: L.C.W., K.G., B.T. V.S.P., L.A.K.; Analysis and/or Interpretation: L.C.W., K.G., B.T. V.S.P., L.A.K.; Literature Search: L.C.W.; Writing: L.C.W., K.G., B.T. V.S.P., L.A.K.

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

Financial Disclosure: This research was supported, in part, by a grant-in-aid from ImpediMed Limited (Brisbane, Australia) to the Australian Lymphoedema Education, Research and Treatment (ALERT) Program, Macquarie University.

References

1. Varghese SA. Secondary lymphedema: Pathogenesis. J Ski Sex Transm Dis. 2021; 3: 7-15. [Crossref]
2. Nassif TM, Brunelle CL, Gillespie TC, Bernstein MC, Bucci LK, Naoum GE, et al. Breast cancer-related lymphedema: a review of risk factors, radiation therapy contribution, and management strategies. Curr Breast Cancer Rep. 2020; 12: 305-316. [Crossref]
3. Nguyen TT, Hoskin TL, Habermann EB, Cheville AL, Boughey JC. Breast Cancer-Related Lymphedema Risk is Related to Multidisciplinary Treatment and Not Surgery Alone: Results from a Large Cohort Study. Ann Surg Oncol. 2017; 24: 2972-2980. (PMID: 28766228) [Crossref]
4. Brunelle CL, Taghian AG. Breast Cancer-Related Lymphedema: Risk Stratification and a Continued Call for Screening. JCO Oncol Pract. 2023; 19: 1081-1083. (PMID: 37816203) [Crossref]
5. Gillespie TC, Sayegh HE, Brunelle CL, Daniell KM, Taghian AG. Breast cancer-related lymphedema: risk factors, precautionary measures, and treatments. Gland Surg. 2018; 7: 379-403. (PMID: 30175055) [Crossref]
6. Koelmeyer LA, Moloney E, Boyages J, Sherman KA, Dean CM. Prospective surveillance model in the home for breast cancer-related lymphoedema: a feasibility study. Breast Cancer Res Treat. 2021; 185: 401-412. (PMID: 33006001) [Crossref]
7. Koelmeyer LA, Borotkanics RJ, Alcorso J, Prah P, Winch CJ, Nakhel K, et al. Early surveillance is associated with less incidence and severity of breast cancer-related lymphedema compared with a traditional referral model of care. Cancer. 2019; 125: 854-862. (PMID: 30521080) [Crossref]

8. Rafn BS, Christensen J, Larsen A, Bloomquist K. Prospective Surveillance for Breast Cancer-Related Arm Lymphedema: A Systematic Review and Meta-Analysis. J Clin Oncol. 2022; 40: 1009-1026. (PMID: 35077194) [Crossref]
9. Skjødt Rafn B, Jensen S, Bjerre ED, Wittenkamp MC, Benjaminsen K, Christensen LP, et al. Prospective surveillance for breast cancer-related lymphedema (PROTECT). Acta Oncol. 2023; 62: 808-813. (PMID: 37042161) [Crossref]
10. Koelmeyer L, Gaitatzis K, Ridner SH, Boyages J, Nelms J, Hughes TM, et al. Implementing a prospective surveillance and early intervention model of care for breast cancer-related lymphedema into clinical practice: application of the RE-AIM framework. Support Care Cancer. 2021; 29: 1081-1089. (PMID: 32613370) [Crossref]
11. Suami H, Heydon-White A, Mackie H, Czerniec S, Koelmeyer L, Boyages J. A new indocyanine green fluorescence lymphography protocol for identification of the lymphatic drainage pathway for patients with breast cancer-related lymphoedema. BMC Cancer. 2019; 19: 985. (PMID: 31640623) [Crossref]
12. Forte AJ, Boczar D, Huayllani MT, Lu X, Ciudad P. Lymphoscintigraphy for Evaluation of Lymphedema Treatment: A Systematic Review. Cureus. 2019; 11: e6363. (PMID: 31886094) [Crossref]
13. Svensson BJ, Dylke ES, Ward LC, Black DA, Kilbreath SL. Screening for breast cancer-related lymphoedema: self-assessment of symptoms and signs. Support Care Cancer. 2020; 28: 3073-3080. (PMID: 31641870) [Crossref]
14. Mayrovitz HN. Measuring Breast Cancer-Related Lymphedema. In: Mayrovitz HN, editor. Breast Cancer [Internet]. Brisbane (AU): Exon Publications; 2022 Aug 6. Chapter 5. (PMID: 36122156) [Crossref]
15. Shah C, Whitworth P, Valente S, Schwarz GS, Kruse M, Kohli M, et al. Bioimpedance spectroscopy for breast cancer-related lymphedema assessment: clinical practice guidelines. Breast Cancer Res Treat. 2023; 198: 1-9. (PMID: 36566297) [Crossref]
16. Ancukiewicz M, Miller CL, Skolny MN, O'Toole J, Warren LE, Jammallo LS, et al. Comparison of relative versus absolute arm size change as criteria for quantifying breast cancer-related lymphedema: the flaws in current studies and need for universal methodology. Breast Cancer Res Treat. 2012; 135: 145-152. (PMID: 22710706) [Crossref]
17. Keeley V. The Early Detection of Breast Cancer Treatment-Related Lymphedema of the Arm. Lymphat Res Biol. 2021; 19: 51-55. (PMID: 33270493) [Crossref]
18. McLaughlin SA, Stout NL, Schaverien MV. Avoiding the Swell: Advances in Lymphedema Prevention, Detection, and Management. Am Soc Clin Oncol Educ Book. 2020; 40: 1-10. (PMID: 32315238) [Crossref]
19. Wiser I, Mehrara BJ, Coriddi M, Kenworthy E, Cavalli M, Encarnacion E, et al. Preoperative Assessment of Upper Extremity Secondary Lymphedema. Cancers (Basel). 2020; 12: 135. (PMID: 31935796) [Crossref]
20. Dylke ES, Ward LC. Three Decades of Bioelectrical Impedance Spectroscopy in Lymphedema Assessment: An Historical Perspective. Lymphat Res Biol. 2021; 19: 206-214. (PMID: 33232645) [Crossref]
21. Gaw RL, Box R, Cornish BH. Bioimpedance in the assessment of unilateral lymphedema of a limb: the optimal frequency. Lymphat Res Biol. 2011; 9: 93-99. (PMID: 21688978) [Crossref]
22. Cornish BH, Chapman M, Hirst C, Mirolo B, Bunce IH, Ward LC, et al. Early diagnosis of lymphedema using multiple frequency bioimpedance. Lymphology. 2001; 34: 2-11. (PMID: 11307661) [Crossref]
23. Koelmeyer LA, Gaitatzis K, Thompson B, Ward LC. Effects of Body Positioning When Assessing Lymphedema of the Lower Limb Using Bioimpedance Spectroscopy. Lymphat Res Biol. 2024; 22: 43-54. (PMID: 37851985) [Crossref]
24. Ward LC, Thompson B, Gaitatzis K, Koelmeyer LA. Comparison of Volume Measurements and Bioimpedance Spectroscopy Using A Stand-on Device for Assessment of Unilateral Breast Cancer-Related Lymphedema. Eur J Breast Health. 2024; 20: 141-148. (PMID: 38571690) [Crossref]
25. Ward LC, Dylke E, Czerniec S, Isenring 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]
26. Wang H, Li D, Liuya J, Dylke ES, Ward LC, Jia J, et al. Reference ranges using bioimpedance for detection of lymphedema in Chinese women. Lymphat Res Biol. 2017; 15: 268-273. (PMID: 28880731) [Crossref]
27. Ridner SH, Bonner CM, Doersam JK, Rhoten BA, Schultze B, Dietrich MS. Bioelectrical impedance self-measurement protocol development and daily variation between healthy volunteers and breast cancer survivors with lymphedema. Lymphat Res Biol. 2014; 12: 2-9. (PMID: 24502422) [Crossref]
28. Jung M, Jeon JY, Yun GJ, Yang S, Kwon S, Seo YJ. Reference values of bioelectrical impedance analysis for detecting breast cancer-related lymphedema. Medicine (Baltimore). 2018; 97: e12945. (PMID: 30383644) [Crossref]
29. Koelmeyer LA, Ward LC, Dean C, Boyages J. Body Positional Effects on Bioimpedance Spectroscopy Measurements for Lymphedema Assessment of the Arm. Lymphat Res Biol. 2020; 18: 464-473. (PMID: 32027213) [Crossref]
30. McLaughlin SA, Brunelle CL, Taghian A. Breast Cancer-Related Lymphedema: Risk Factors, Screening, Management, and the Impact of Locoregional Treatment. J Clin Oncol. 2020; 38: 2341-2350. (PMID: 32442064) [Crossref]
31. Ridner SH, Dietrich MS, Cowher MS, Taback B, McLaughlin S, Ajkay N, et al. A Randomized Trial Evaluating Bioimpedance Spectroscopy Versus Tape Measurement for the Prevention of Lymphedema Following Treatment for Breast Cancer: Interim Analysis. Ann Surg Oncol. 2019; 26: 3250-3259. (PMID: 31054038) [Crossref]
32. Qin ES, Bowen MJ, Chen WF. Diagnostic accuracy of bioimpedance spectroscopy in patients with lymphedema: A retrospective cohort analysis. J Plast Reconstr Aesthet Surg. 2018; 71: 1041-1050. (PMID: 29650264) [Crossref]
33. Hayes SC, Janda M, Ward LC, Reul-Hirche H, Steele ML, Carter J, et al. Lymphedema following gynecological cancer: Results from a prospective, longitudinal cohort study on prevalence, incidence and risk factors. Gynecol Oncol. 2017; 146: 623-629. (PMID: 28624154) [Crossref]
34. Steele ML, Janda M, Vagenas D, Ward LC, Cornish BH, Box R, et al. Normative Interlimb Impedance Ratios: Implications for Early Diagnosis of Uni- and Bilateral, Upper and Lower Limb Lymphedema. Lymphat Res Biol. 2018; 16: 559-566. (PMID: 30280970) [Crossref]
35. Ward L, Winall A, Isenring E, Hills A, Czerniec S, Dylke E, et al. Assessment of bilateral limb lymphedema by bioelectrical impedance spectroscopy. Int J Gynecol Cancer. 2011; 21: 409-418. (PMID: 21270623) [Crossref]
36. Russo S, Walker JL, Carlson JW, Carter J, Ward LC, Covens A, et al. Standardization of lower extremity quantitative lymphedema measurements and associated patient-reported outcomes in gynecologic cancers. Gynecol Oncol. 2021; 160: 625-632. (PMID: 33158510) [Crossref]
37. York SL, Ward LC, Czerniec S, Lee MJ, Refshauge KM, Kilbreath SL. Single frequency versus bioimpedance spectroscopy for the assessment of lymphedema. Breast Cancer Res Treat. 2009; 117: 177-182. (PMID: 18563555) [Crossref]
38. Dylke E. Measurement of breast cancer-related lymphoedema. J Physiother. 2022; 68: 238-243. (PMID: 36244958) [Crossref]

Original Article

Eur J Breast Health 2024; 20(4): 258-261
DOI: 10.4274/ejbh.galenos.2024.2024-5-9

Mastalgia and Why It Should Be Evaluated With Imaging in Areas Where Use of Breast Cancer Screening Services are Unsatisfactory

Shivangi Tomar[1], Akhilendra Singh Parihar[2], Sanjay Kumar Yadav[3], Rekha Agrawal[1]

[1]Department of Radiodiagnosis, NSCB Medical College, Jabalpur, India
[2]Department of Pediatrics, NSCB Medical College, Jabalpur, India
[3]Department of Surgery, NSCB Medical College, Jabalpur, India

ABSTRACT

Objective: Mastalgia or breast pain is a very common symptom in women attending breast clinic. The aim of this study was to evaluate whether imaging for mastalgia leads to cancer detection in an area where routine breast cancer screening services are underutilized.

Materials and Methods: This prospective study was performed between 1st March 2021 to 31st January 2023 at a tertiary care academic institution of central India. All patients underwent through clinical examination by a surgeon. Then patients were referred for ultrasound and/or X-ray mammography (MMG) depending on age. Cancer detection rate was calculated.

Results: The final cohort consisted of 176 patients with mastalgia and without any abnormality on clinical breast examination. Sixteen patients had mass lesion on radiology and core needle biopsy resulted as infiltrating duct carcinoma in 7 patients and benign phylloides tumor in one patient. Overall case detection rate for cancer was 4%.

Conclusion: The breast cancer detection rate in patients presenting with mastalgia was low. However, in the absence of routine mammographic screening in the Indian general population, these would have been missed. Hence, diagnostic assessment for mastalgia is an appropriate strategy in countries where routine screening MMG is lacking.

Keywords: Mastalgia; breast cancer; screening; mammography

Cite this article as: Tomar S, Parihar AS, Yadav SK, Agrawal R. Mastalgia and Why It Should Be Evaluated With Imaging in Areas Where Use of Breast Cancer Screening Services are Unsatisfactory. Eur J Breast Health. 2024; 20(4): 258-261

Key Points

- Mastalgia is the most common presenting complaint in breast clinics.
- Imaging is usually not recommended if clinical examination is normal.
- However, in countries where routine screening is not available, imaging can lead to early breast cancer detection.

Introduction

Mastalgia or breast pain is a very common symptom in women attending breast clinic and it is thought to occur in up to 60–70% of women in their lifetime (1-3). Exact etiopathogenesis of mastalgia is not well understood and is multifactorial (2, 4). Guidelines for evaluation and treatment of mastalgia remain controversial. The American College of Radiology (ACR) Practice Guidelines suggests diagnostic imaging only for a persistent and focal area of pain, defined as involving 25% of the breast and axillary tissue (4, 5). Many centres, including ours, prefer to image all patients presenting with mastalgia (6). Many other studies have reported that such imaging evaluation for patients with mastalgia leads to unnecessary biopsies, increased costs, patient anxiety and overutilization of healthcare resources (7, 8).

The aim of this study was to evaluate whether imaging for mastalgia leads to cancer detection in an area where routine breast cancer screening services are underutilized.

Materials and Methods

This prospective study was performed between 1st March 2021 and 31st January 2023, at a tertiary care academic institution in central India after approval by Netaji Subhash Chandra Bose Medical College

Corresponding Author:
Rekha Agrawal; drrekhajabalpur@gmail.com

Received: 13.06.2024
Accepted: 17.07.2024
Available Online Date: 26.09.2024

Jabalpur Institutional Ethics Committee (decision no: IEC/2020-23, date: 07.012021). Informed consent was obtained from patients.

Inclusion criteria were age above 18 years and all patients presenting with mastalgia irrespective of focality, duration, or cyclical nature. Patients with any abnormal clinical finding, such as palpable mass, nipple discharge or history of breast implant were excluded. Patients were evaluated as per department protocol. All patients underwent through clinical examination by a trained breast surgeon. Then patients are referred for ultrasound (USG) and/or X-ray mammography (MMG) depending on age, usually on the same day or the next day. Women less than 30 years of age underwent USG alone while between 30 to 40 years of age underwent additional MMG in case of any abnormal finding on USG and patients above 40 years underwent MMG alone (plus USG if any abnormal finding on MMG). The radiologist was not blinded with regards to symptoms and had over 10 years experience. In India, there is no national guidelines for population-based screening MMG. Women may visit a medical centre and request for a regular screening MMG.

Imaging Technique and Interpretation

The sonographic examination of breast and axilla was performed using a high frequency linear probe with frequency range 7–12 MHz (Alpinion E-CUBE -i7, Magokjungang 14-ro, Gangseo-gu, Seoul, Republic of Korea). MMG was done using MMG system 3000 Nova (Siemens Healthcare Private Limited Vikhroli East, Mumbai – 400 079, India). The patients were positioned supine with the arm on the side of interest relaxed up by the side of the head. Both the breast were exposed and all quadrant were examined by sweeping the transducer in radial and anti-radial direction to visualise the abnormality. Both axillae were also examined for any mass extension or lymph node abnormality. Lesions were also examined under color Doppler USG and results were noted. Examinations were interpreted by two dedicated breast radiologists using the ACR Breast Imaging-Reporting Data System (BI-RADS) lexicon (9). Histopathological samples for diagnosis were obtained under USG (routinely a 14-gauge core needle device) guideance, if indicated.

Statistical Analysis

The data of the present study was recorded in Microsoft excel sheet. Descriptive statistics and *Z* test was used to compare patient demographics, pain characteristics, and imaging modality between all patients/cases and those with breast cancer. All analysis was performed using SPSS software (IBM Inc., Armonk, NY, USA). *P* values less than 0.05 were considered statistically significant.

Results

A total of 292 women presented with mastalgia during the study period. Of these, 116 patients were excluded; 33.9% (99/292) had an associated palpable abnormality and 5.8% (17/292) had a skin/nipple abnormality. The final cohort consisted of 176 patients with mastalgia and without any abnormality on clinical breast examination. Baseline demographics are presented in Table 1. The frequency (%) of various BI-RADS categories by MMG and USG is provided in Table 2.

Sixteen (9.1%) patients had mass lesion on radiology and core needle biopsy results were infiltrating duct carcinoma in 7 patients (early breast cancer) and benign phylloides tumor in one patient. Remaining 8 patients had benign pathology. Overall case detection rate for cancer was 4%. The median (range) age of patients diagnosed with cancer was 38 (22–58) years. Patients diagnosed with malignancy were older compared to the overall patient population (mean 39±8.5 *vs.* 34.4±6.8 years, $p = 0.06$) and none of the patients had personnel history of breast cancer.

In the cohort, 45% had cyclical pain and 55% non-cyclical pain. The proportion of patients with focal pain was 44% whereas the remainder (56%) had diffuse pain. Unilateral pain occurred in 47% cases whereas in 53% pain was bilateral. No statistically significant differences in pain characteristics were noted between the whole cohort with breast pain and those who were diagnosed with malignancy.

Discussion and Conclusion

In this cohort of patients where routine screening MMG is lacking, the case detection rate for breast cancer was 4% in patients presenting with mastalgia and without any palpable findings. The age group of patients diagnosed with malignancy was similar to the age group of patients without malignancy. All diagnosed patients had no familial risk factor.

Table 1. Patient demographics and frequency details

Variable	
Age, mean ± SD	34.4±6.8 years
<31 years	37
30–40 years	25
41–50 years	24
>51 years	13
Mastalgia	
Left breast	94 (53.40%)
Right breast	69 (39%)
Bilateral	13 (7.39%)
Breast density	
Extremely dense	19 (11%)
Heterogeneously dense	72 (41%)
Scattered fibro-glandular density	60 (34%)
Fatty	25 (14%)

SD: Standard deviation

Table 2. The frequency (%) of various BI-RADS categories by mammogram and ultrasound

BI-RADS category	By mammogram (%)	By ultrasound (%)
1	88 (70%)	93 (53%)
2	14 (11%)	53 (30%)
3	6 (5%)	18 (10%)
5	3 (2%)	12 (7%)
0	15 (12%)	-
Total	126 (100%)	176 (100%)

BI-RADS: Breast Imaging-Reporting Data System

Breast cancer has some striking differences in Asian women compared to their western counterparts (10). Although its incidence is increasing rapidly worldwide, the highest increase in incidence is seen in Asian countries (10, 11). Age at diagnosis is lower in Asian countries, which is true in India as well. The median age of patients from India has been reported to range from 35 to 45 years (12-14). Breast cancer in Indian women is also more aggressive, with a high proportion of triple negative breast cancers (14, 15). Despite being the most common cancer in India, onset at younger age and aggressive nature, there is no mandatory screening MMG in India. Hence any patient presenting with a breast complaint is also an opportunity to screen her for breast cancer. Our results showed that 4% of patients with mastalgia as the presenting complaint were ultimately diagnosed with breast cancer.

Multiple studies have evaluated the role of imaging in mastalgia. A study from Canada found 0.4% CDR in women with mastalgia and concluded that imaging for isolated breast pain is unnecessary and overutilization of healthcare resources. However, they recommended routine screening MMG to be encouraged (16). Another study among American women concluded that focal breast pain is rarely associated with malignancy and imaging should be deferred if there are no other clinical findings, and a negative mammogram (17). A study from the United Kingdom also showed that pain is not a frequent symptom of breast cancer (6). However, these authors recommended that direct testing with MMG would be safe, effective and efficient practice. All these studies advising against imaging for mastalgia, are from high income countries and have a screening MMG program. Unfortunately, this is not the case with India. More so, our center is located in central India having a high proportion of underprivileged citizens in the population. For these patients, imaging of the breast when they come to clinic for mastalgia, can be the only time when they undergo screening and it should be utilized.

Our study has several limitations. As it was conducted at a tertiary academic institution our results may not be generalizable. Referral bias is another limitation, as general practitioners and hospitalists do not always refer patients with mastalgia. Clinical examination was also performed by multiple surgeons. Both USG and MMG was performed in women over 30 years at the discretion of surgeon/radiologist and a very small number of patients underwent both examinations. Study would have been more significant in terms of which imaging modality to prefer if both USG and MMG were done in all patients and few cancers were missed in one modality but detected on other. Consequently, we would have been able to make recommendations about the benefits of USG in the setting of a negative mammogram, but this was not possible. Another limitation was the low number of cancer detected. However, to the best of our knowledge, ours is the largest study with largest proportion of cancers detected in evaluation of mastalgia from India.

The breast cancer detection rate in patients presenting with mastalgia was low at 4%. However, in the absence of routine mammographic screening in Indian general population, these cases of breast cancer would otherwise have been missed. Hence, diagnostic assessment for mastalgia is an appropriate strategy in countries where routine screening MMG is lacking.

Ethics Committee Approval: Approval by Netaji Subhash Chandra Bose Medical College Jabalpur Institutional Ethics Committee (decision no: IEC/2020-23, date: 07.012021).

Informed Consent: Informed consent was obtained from patients.

Authorship Contributions: Surgical and Medical Practices: S.T., A.S.P., S.K.Y., R.A.; Concept: S.T., A.S.P., S.K.Y., R.A.; Design: S.T., A.S.P., S.K.Y., R.A.; Data Collection and/or Processing: S.T., A.S.P., S.K.Y., R.A.; Analysis and/or Interpretation: S.T., A.S.P., S.K.Y., R.A.; Literature Search: S.T., A.S.P., S.K.Y., R.A.; Writing: S.T., A.S.P., S.K.Y., R.A.

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

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

References

1. Ader DN, Shriver CD. Cyclical mastalgia: prevalence and impact in an outpatient breast clinic sample. J Am Coll Surg. 1997; 185: 466-470. (PMID: 9358091) [Crossref]
2. Kataria K, Dhar A, Srivastava A, Kumar S, Goyal A. A systematic review of current understanding and management of mastalgia. Indian J Surg. 2014; 76: 217-222. (PMID: 25177120) [Crossref]
3. Scurr J, Hedger W, Morris P, Brown N. The prevalence, severity, and impact of breast pain in the general population. Breast J. 2014; 20: 508-513. (PMID: 25041468) [Crossref]
4. Jokich PM, Bailey L, D'Orsi C, Green ED, Holbrook AI, Lee SJ, et al. ACR Appropriateness Criteria® breast pain. J Am Coll Radiol. 2017; 14: S25-S33. (PMID: 28473081) [Crossref]
5. Holbrook AI, Moy L, Akin EA, Baron P, Didwania AD, Heller SL, et al. ACR Appropriateness Criteria® Breast pain. https://acsea rch.acr.org/docs/30915 46/Narra tive/. American College of Radiology. Accessed 1 Feb, 2023. [Crossref]
6. Cook N, Batt J, Fowler C. Symptomatic Breast Cancers and Why Breast Pain May not Always Need Clinical Review. Eur J Breast Health. 2020; 16: 267-269. (PMID: 33062967) [Crossref]
7. Howard MB, Battaglia T, Prout M, Freud K. The effect of imaging on the clinical management of breast pain. J Gen Intern Med. 2012; 27: 817-882. (PMID: 22331398) [Crossref]
8. Arslan M, Kucukerdem HS, Can H, Tarcan E. Retrospective analysis of women with only mastalgia. J Breast Health 2016; 12: 151-154. (PMID: 28331753) [Crossref]
9. Sickles EA, D'Orsi CJ, Bassett LW et al. ACR BIRADS ® mammography. In: D'Orsi CJ, Sickles EA, Mendelson EB et al (eds) ACR BI-RADS® atlas, breast imaging reporting and data system, 5th edn. American College of Radiology, Reston, VA, 2013. [Crossref]
10. Leong SP, Shen ZZ, Liu TJ, Agarwal G, Tajima T, Paik NS, et al. Is breast cancer the same disease in Asian and Western countries? World J Surg. 2010; 34: 2308-2324. (PMID: 20607258) [Crossref]
11. Green M, Raina V. Epidemiology, screening and diagnosis of breast cancer in the Asia–Pacific region: current perspectives and important considerations. Asia Pacific J Clin Oncol. 2008; 4(Suppl 3): S5-S13. [Crossref]
12. Sharma M, Sharma JD, Sarma A. Triple negative breast cancer in people of North East India: critical insights gained at a regional cancer centre. Asian Pac J Cancer Prev. 2014; 15: 4507-4511. (PMID: 24969877) [Crossref]

13. Sen S, Gayen R, Das S, Maitra S, Jha A, Mahata M. A clinical and pathological study of triple negative breast carcinoma: experience of a tertiary care centre in eastern India. J Indian Med Assoc. 2012; 110: 686-689, 705. (PMID: 23738399) [Crossref]

14. Anand A, Mishra A, Damde H, Saxena A, Yadav SK, Sharma D. Molecular Profile and Clinico-pathological Characteristics of Breast Cancer in Central India: First Investigative Report. Indian J Surg Oncol. 2022; 13: 421-425. Epub 2022 Jan 14. (PMID: 35782821) [Crossref]

15. Rathod V, Jha CK, Sinha U, Singh PK, Kumar A, Bhadani PP, et al. First Comprehensive Report of Clinicopathological Profile of Breast Cancer from Bihar, India. Indian J Surg Oncol. 2021; 12: 598-602. (PMID: 34658590) [Crossref]

16. Mohallem Fonseca M, Lamb LR, Verma R, Ogunkinle O, Seely JM. Breast pain and cancer: should we continue to work-up isolated breast pain? Breast Cancer Res Treat. 2019; 177: 619-627. (PMID: 31309396) [Crossref]

17. Owen WA, Brazeal HA, Shaw HL, Lee MV, Appleton CM, Holley SO. Focal breast pain: imaging evaluation and outcomes. Clin Imaging. 2019; 55: 148-155. (PMID: 30825809) [Crossref]

Original Article

Eur J Breast Health 2024; 20(4): 262-269
DOI: 10.4274/ejbh.galenos.2024.2024-3-4

Dietary Patterns and Breast Cancer Risk: A KCPS-II Cohort Study

Ji-Young Lee, Hae In Cho, Heejin Kimm

Department of Epidemiology and Health Promotion, Institute for Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Korea

ABSTRACT

Objective: There have been inconsistencies in the evidence for a role of dietary patterns in the development of breast cancer. In this study, we used a large-scale cohort [Korean Cancer Prevention Study-II (KCPS-II)] to examine the association between dietary patterns and breast cancer risk in Korean women.

Materials and Methods: The dietary patterns of 14,807 women from the KCPS-II were derived by factor analysis and 135 cases of breast cancer were diagnosed during the follow-up period. Cox proportional models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of breast cancer.

Results: The following three major dietary patterns were identified: "Korean dietary pattern" (high intake of Kimchi, vegetables, and rice); "sweet dietary pattern" (high intake of soda and sugar); and "new (Western-like) dietary pattern" (high intake of dairy products, eggs, oil, fruits, and bread). After adjusting for potential confounders, neither the Korean (HR for the highest compared with the lowest tertile, 1.04; 95% CI 0.53–2.06) nor the sweet dietary patterns were associated with the risk of breast cancer. In contrast, the new (Western-like) dietary pattern was found to be significantly associated with an increased risk of breast cancer with an HR (95% CI) of 1.01 (0.65–1.60) for the second tertile and 1.61 (1.04–2.50) for the third tertile as compared with the lowest tertile. After stratifying by menopausal status, these effects were only statistically significant among premenopausal women for the third tertile, compared with those in the bottom tertile (HR 1.69; 95% CI 1.06–2.68; p = 0.028). No significant association was observed between the Korean or sweet dietary pattern and breast cancer among either pre- or postmenopausal women.

Conclusion: Our findings revealed that a greater consumption of a new (Western-like) diet was associated with an increased breast cancer risk and consequently offer a potential prevention strategy for Korean women.

Keywords: Dietary pattern; breast cancer; KCPS-II cohort; Korean women

Cite this article as: Lee J-Y, Cho HI, Kimm H. Dietary Patterns and Breast Cancer Risk: A KCPS-II Cohort Study. Eur J Breast Health. 2024; 20(4): 262-269

Key Points

- Dietary patterns of 14,807 women from Korean Cancer Prevention Study-II were derived using factor analysis, and 135 cases of breast cancer were diagnosed during the follow-up period.
- Three major dietary patterns were identified: "Korean dietary pattern" (high intake of kimchi, vegetables, and rice), "sweet dietary pattern" (high intake of soda and sugar), and "new (Western) dietary pattern" (high intake of dairy products, eggs, oil, fruits, and bread).
- The Western diet was associated with an increased breast cancer risk, and reducing the consumption of Western diet may be a potential prevention strategy for Korean women.

Introduction

Breast cancer is one of the leading causes of death in women globally (1). It was among the most commonly diagnosed types of cancer in Korean women: 22,300 new cases were reported by the Korea Central Cancer Registry in 2017 (2). The age-specific incidence rate has been steadily increasing from 21.4 per 100,000 in 1999 to 55.6 per 100,000 in 2017 (2). Although several epidemiologic studies have examined the association between nutrient intake and breast cancer risk (3), their results have been inconsistent (4-6). Therefore, researchers have recently recognized the importance of identifying dietary patterns, following a holistic approach, rather than individual nutrients, in their contribution to chronic disease (7). Not only are such patterns practical tools for developing dietary recommendations but also a valuable method to determine risk factors and prevent disease simultaneously (8). Recently, prospective epidemiologic studies have examined associations

Corresponding Author:
Ji-Young Lee; newwd7@gmail.com

Received: 11.07.2024
Accepted: 24.07.2024
Available Online Date: 26.09.2024

between certain dietary patterns and breast cancer risk (9-13). However, most studies have been conducted in European populations, and only a few studies have investigated this relationship in Asian populations (14, 15). In addition, Zhang et al. (16) reported that a diet high in vegetables, fruits, and soy could decrease breast cancer risk, while Cui et al. (17) reported that this was not true for a vegetable-soy pattern, suggesting an inconsistency in results. Thus, this study aimed to identify dietary patterns and examine their association with the risk of developing breast cancer using a large-scale cohort study [Korean Cancer Prevention Study-II (KCPS-II)].

Materials and Methods

Study Population

The KCPS-II is a prospective cohort study initiated in April 2004 supported by the Seoul city government as a part of the Korean Metabolic Syndrome Research Initiative study (18). Participants received routine health assessments at 18 health promotion centers across South Korea. The number of retrospectively enrolled KCPS-II participants based on health examination records between 1994 and 2005 is 270,514; data from 192,358 participants was prospectively collected between 2004 and 2013. After excluding participants with missing information on lifestyle and dietary habits, as well as those who were male or had a history of breast cancer, a total of 14,807 participants were included for final analyses (Figure 1). Of 67,271 female cohort member with data collection from 2004–2013, a very large proportion (78%) had missing dietary data because only surveys in institutions with professional dietitians were available.

Cancer information was ascertained by linkages to the Korea Central Cancer Registry, until 31 December 2018. Cancer incidence was identified based on the 10th revision of International Classification of Disease. Our health examinations included questions on lifestyle, family, and personal medical history in addition to an assessment of anthropometric and clinical factors. General demographic and lifestyle variables including age, sex, education level, smoking status, and alcohol intake were collected by a standardized questionnaire; we also deployed a short version of the food-frequency questionnaire (FFQ). The Yonsei University Health System Institutional Review Board approved the study (decision no: Y-2020-0142, date: 05.10.2020), and all participants provided written, informed consent prior to participation.

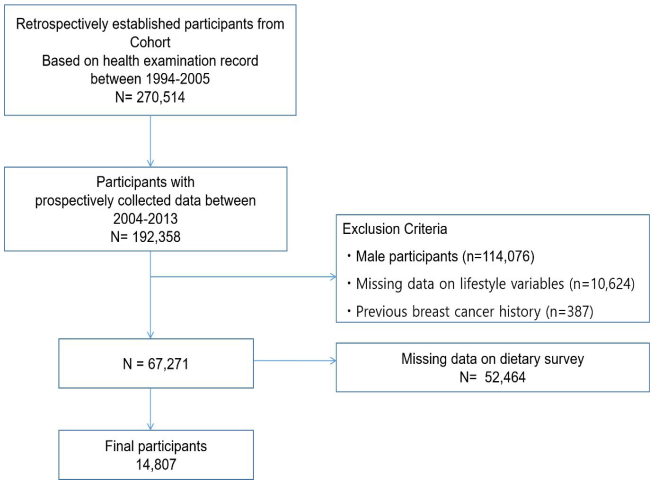

Figure 1. Flow diagram for study participants

Assessment of Dietary Intake and Risk Factors

A brief dietary assessment evaluated and validated in a previous study was used for estimating dietary patterns (19). This assessment comprised a short version of the FFQ, which is suitable to identify relationships between dietary intake and disease risk (20). It consists of 17 food items based on seven food groups: (1) fish, meat, eggs, and soybean products; (2) milk and dairy products; (3) vegetables; (4) fruits; (5) cereals and potatoes; (6) sugars and candies; and (7) fats and oil. Daily nutrient intakes were calculated based on food consumption: Participants were asked to fill out the frequency of their current intake of each food item according to four categories (0: never, 0.5: often, 1.0: regular, 1.5: always sufficient). Well trained dietitians asked participants how often they had consumed 17 food items in the morning, afternoon, and evening. Study participants were informed that the frequency of dietary intake in categories of always sufficient was assigned in reference to a regular frequency according to dietitian's instruction. The amounts of each food consumed are estimated in reference to a common size container (e.g., bowls, cups, and glasses), standard measuring cups and spoons such as photographs. Study participants were interviewed by a trained dietitian, who used instruments for estimating portion sizes according to the list of food exchanges for Korea. The third edition of food exchange lists was revised in 2010 by the Korean Diabetes Association, the Korean Nutrition Society, the Korean Society of Community Nutrition, the Korean Dietetic Association and the Korean Association of Diabetes Dietetic. Each participant's age, regular exercise habit (yes, no), alcohol intake (never, ex-drinkers, current drinkers), smoking status (never, ex-smokers, current smokers), menopausal status (pre-menopausal or postmenopausal), age at menarche, and the presence of family history of cancer (no, yes) were obtained using the questionnaire. We obtained information on the participant's height (cm) and weight (kg) directly measured by the medical staff. The body mass index (BMI) (kg/m^2) was calculated by dividing the body weight (kg) by the square of height (m).

Statistical Analysis

General characteristics of study participants stratified by breast cancer incidence outcome were compared using Student's t-test and chi-square test. Cox proportional hazards model with person-years was used to evaluate the hazard ratio (HR) and 95% confidence interval (CI) of breast cancer risk for each three dietary patterns. Multivariable HRs were adjusted for age (continuous), total energy intake (kcal/day, continuous), educational level (middle school or less, high school or college, undergraduate or more), exercise (yes, no), smoking status (never, ex-smokers, current smokers), alcohol intake (never, ever, current), and the menopausal status (pre-menopausal, postmenopausal). We used multivariable Cox proportional hazards regression models to examine the HRs and 95% CI for breast cancer risk across the tertile categories of each dietary pattern score, taking the lowest tertile category as reference. Principal factor analysis was used to cluster factors, followed by orthogonal (Varimax) rotation to assist in interpretation of the factors (PROC FACTOR and Varimax options). The principal factor analysis requires the number of clusters to be specified in advance and generates mutually exclusive clusters by comparing Euclidean distances between each subject and each cluster center in an interactive process using a K-means method (20). The SAS statistical package for Windows (version 9.4, SAS) was used for all statistical analyses. P<0.05 was considered significant. Food groups with an absolute loading greater than 0.3 on a given factor were considered to contribute importantly to that factor. We determined

three factors by eigenvalues of >1.1 and a scree plot and interpretability of the derived factors. We presented the distributions of each food item for the three dietary patterns (Supplementary Table 1). The final number of clusters was selected as 3-cluster by comparing between cluster variance and within-cluster variance ratios.

Results

The results derived from the factor loading matrix for major dietary patterns are depicted in Table 1. We extracted three major dietary patterns from the KCPS-II cohort. Based on the predominant food groups, we labeled these three patterns the "Korean dietary pattern", the "sweet dietary pattern", and the "New (Western-like) dietary pattern". The Korean pattern comprised a high content of meat, fish, tofu, herbs, vegetables, kimchi, rice, bread, and noodles; the sweet dietary pattern contained two food groups that consisted of sugar (honey) and soda; the new pattern featured a high load of eggs, milk, dairy products, oil, bread, snacks, and fruits. The total variances of the Korean, sweet, and new dietary patterns were 1.9%, 1.6%, and 1.6%, respectively.

Table 2 summarizes the general characteristics of study participants stratified by breast cancer incidence. Among the total of 14,807 women included for final analysis, 135 were diagnosed with breast cancer

Table 1. Factor loading matrix for the three major dietary patterns (*n* = 14,807)

Food group	Korean	Sweet	New (Western-like)
Meat, fish, tofu	0.62407		
Eggs			0.68750
Milk and dairy products			0.47546
Herbs and vegetables	0.65056		
Kimchi	0.73593		
Rice, bread, noodles	0.69294		
Oil			0.66155
Sugar and honey		0.83046	
Soda		0.82371	
Bread and snacks			0.40228
Fruits			0.43916
Variance explained by each factor	1.9108947	1.6446474	1.5862974

Factor loading scores less than 0.3 are not shown

Table 2. General characteristics of study participants

	No breast cancer *n* = 14,672	Incident breast cancer *n* = 135	*p*-value
	Mean (SD)	Mean (SD)	
Age (year)	46.39 (11.07)	46.97 (8.96)	0.46
Education (year)	13.2 (3.51)	14.0 (3.25)	0.00
Height (cm)	157.93 (5.49)	158.91 (5.66)	0.04
Body mass index (kg/m^2)	23.04 (3.09)	22.79 (2.88)	0.36
Family history of breast cancer (%)	3.21	0.00	0.59
Age in years at menarche (year)	14.90 (1.86)	14.74 (1.99)	0.46
Menopausal status (%)			
Pre-menopausal	93.30	91.85	
Postmenopausal	6.70	8.15	0.50
Amount of alcohol drinking (g/day)	5.16 (19.92)	7.79 (24.92)	0.26
Smoking status (yes/no, %)	4.58	8.15	0.04
Alcohol drinking (yes/no, %)	38.92	40.74	0.65
Use of oral contraceptives (%)	17.77	22.81	0.32
Total energy intake (kcal)	1.728 (311)	1.718 (303)	0.71
Follow-up (years)	8.43 (4.73)	6.69 (4.51)	<0.0001

SD: Standard deviation

during a mean follow-up of 8.15 years. Education, height, and smoking status showed statistically significant differences between non-breast cancer and breast cancer patients. Table 3 shows HRs between the three dietary patterns and breast cancer risk in multivariable analysis. The new dietary pattern was significantly associated with an increased risk of breast cancer by HR (95% CI), which was 1.01 (0.65–1.60) for the second tertile and 1.61 (1.04–2.50) for the third tertile compared with the bottom tertile. However, the Korean and sweet dietary patterns showed no statistically significant association with breast cancer risk in multivariable analysis.

Multivariable HRs of breast cancer according to menopausal status are shown in Table 4. In premenopausal women, multivariable HRs for the new pattern were significantly associated with an increased risk of breast cancer; when comparing the highest with the lowest tertile of the new dietary pattern, the HR was 1.69 (95% CI 1.06–2.68).

Table 3. Breast cancer risk with multivariable Cox proportional hazard model

Variables		HR (95% CI)*	*p*-value	*p*-trend
	Tertile 1	1.0		
Korean dietary patterns	Tertile 2	1.17 (0.73–1.89)	0.51	
	Tertile 3	1.04 (0.53–2.06)	0.90	0.51
	Tertile 1	1.0		
Sweet dietary patterns	Tertile 2	1.11 (0.72–1.71)	0.62	
	Tertile 3	1.13 (0.73–1.75)	0.58	0.45
	Tertile 1	1.0	0.95	
New (Western-like) dietary patterns	Tertile 2	1.01 (0.65–1.60)		
	Tertile 3	1.61 (1.04–2.50)	0.01	0.01

*HR (95% CI) adjusted for age (continuous), total energy intake (kcal/day, continuous), educational duration (years), exercise (yes, no), alcohol intake (never, ever, current), smoking status (never, ex-smokers, current smokers), and the menopausal status (pre-menopausal, postmenopausal); HR: Hazard ratio; CI: Confidence interval

Table 4. Hazard ratio of breast cancer risk by menopausal status

Variables		HR (95% CI)*	*p*-value
Pre-menoposal			
	Tertile 1	1.0	
Korean dietary patterns	Tertile 2	1.12 (0.68–1.83)	0.66
	Tertile 3	0.98 (0.48–1.98)	0.95
	Tertile 1	1.0	
Sweet dietary patterns	Tertile 2	1.01 (0.64–1.59)	0.96
	Tertile 3	1.13 (0.72–1.78)	0.59
	Tertile 1	1.0	
New (Western-like) dietary patterns	Tertile 2	1.09 (0.67–1.75)	0.74
	Tertile 3	1.69 (1.06–2.68)	0.03
Postmenopausal			
	Tertile 1	1.0	
Korean dietary patterns	Tertile 2	4.35 (0.42–44.90)	0.22
	Tertile 3	3.61 (0.21–63.34)	0.38
	Tertile 1	1.0	
Sweet dietary patterns	Tertile 2	2.68 (0.64–11.27)	0.18
	Tertile 3	0.87 (0.14–5.65)	0.89
	Tertile 1	1.0	
New (Western-like) dietary patterns	Tertile 2	0.68 (0.13–3.56)	0.64
	Tertile 3	1.34 (0.33–5.42)	0.68

*HR (95% CI) adjusted for age (continuous), total energy intake (100 kcal/day, continuous), educational duration (years), exercise (yes, no), alcohol intake (never, ever, current), smoking status (never, ex-smokers, current smokers); HR: Hazard ratio; CI: Confidence interval

However, this pattern showed no statistically significant association with breast cancer risk among postmenopausal women.

In addition, the Korean and sweet dietary patterns were not associated with the risk of breast cancer after adjusting for lifestyle factors (smoking status, exercise, and alcohol drinking), total calorie intake, and age among either pre- or postmenopausal women.

Discussion and Conclusion

In the present study we identified three major dietary patterns: Korean, sweet, and new (Western-like). We found that a higher consumption of a new diet was significantly associated with an increased risk of developing breast cancer. This study confirms the international concept that Western diet, along with other sociocultural habits, is associated with an increase incidence of breast cancer in Eastern populations, particularly among young women. However, there were no associations between the Korean or the sweet dietary pattern and breast cancer risk among Korean women.

Previous cohort studies on the association between dietary patterns and breast cancer risk have been predominantly conducted in European populations (9, 21, 22) and the results have been inconsistent. A recent meta-analysis suggested that a Western-like diet may be associated with an increased risk of breast cancer, whereas a prudent dietary pattern was associated with a reduced risk of breast cancer (23). Dietary patterns are likely to vary among different populations due to cultural preferences, geographic characterization, socioeconomic status, and food accessibility (24). Besides, heterogeneity in components of dietary patterns and deviations in measurement methods between studies could have contributed to these inconsistent findings. In our study, we identified a new dietary pattern, characterized by a high intake of dairy products, oil, bread, and fruit in Korean women, and high consumption according to this pattern was significantly associated with the risk of breast cancer. Based on our previous cohort study (19), the consumption of Korean traditional foods, such as vegetables and cereals, has decreased, whereas a new dietary pattern has emerged among Korean adults, whereby the intake of dairy products and fruits has increased. According to the statistics of Korea National Health and Nutrition Examination Survey (2010) (25), less than 40% of the protein intake is derived from animal sources, while in the past, less than 10% of protein intake came from animal sources. It is important to note that the new (Western-like) dietary pattern identified in our study differs from that in others in several aspects. Although among European populations this diet is characterized by a high intake of red and processed meats (26, 27), which may contain pro-carcinogenic factors, such as heterocyclic amines and N-nitroso compounds, the major components of the new (Western-like) dietary pattern in this study were eggs, oil, bread, and dairy products. This pattern is consistent with that found in our previous study, in that the Western and "New" diets were characterized by a high consumption of eggs, oil, soda, fruits,dairy products, and potatoes using factor analysis in Korean women (19). Thus, the current Korean diet has dramatically shifted from the traditional foods to a New dietary pattern, which along with the economic development and globalization supports our observations (28).

In addition, most prospective studies found significant associations between Western dietary patterns and breast cancer risk among postmenopausal (9, 10, 15, 29), but not premenopausal women, although the etiology is still unclear. In contrast, in the current study, stratified-analyses showed that the positive association between a new (Western-like) dietary pattern and breast cancer risk was statistically significant among pre-menopausal, but not postmenopausal women. Given one of the obvious differences between pre- and postmenopausal women, the elevated levels of estrogen may be one plausible explanation for the impact a new (Western-like) dietary pattern has on the risk of developing breast cancer. One potential biological mechanism that the new (Western-like) dietary pattern, characterized by high intakes of energy, animal fat, and refined carbohydrates is through increased BMI and thereby increased levels of estrogen (23). A migration study of Asian-American women suggested that the dietary habits in early adult life may strongly affect breast cancer risk (30). Dietary fat intake was reported to affect endogenous hormones, which regulates ductal morphogenesis (31, 32). Previous studies on mammographic density have also shown the possible importance of early-life diet (saturated fat intake) in breast cancer risk (33).

A new (Western-like) dietary pattern is associated with increased breast cancer risk that needs further study in order to clarify the underlying mechanisms. Although many epidemiologic studies investigating the association between vegetable intake and breast cancer risk yielded inconsistent results, prudent dietary patterns characterized by an intake of vegetables and fruits have been assumed to decrease the breast cancer risk due to anti-oxidative effects (34, 35). However, in this study, we found no significant association between the Korean dietary pattern, which was mainly characterized by high intake of kimchi (spicy cabbage), rice, and vegetables, and breast cancer risk among pre- and postmenopausal women. This is in line with a prospective study among Japanese women, which identified three dietary patterns: "vegetable pattern" (vegetables, potatoes, seaweed, tofu, fruits, fresh fish, eggs, and miso soup); "animal food pattern" (meat, deep-fried foods, fried vegetables, fish paste, and salt-preserved fish); and "dairy product pattern" (milk, dairy products, fruits, coffee, and tea) (15). The authors found that the animal food pattern was significantly associated with a decreased risk of breast cancer morbidity, whereas no significant association was observed between the vegetable and dairy product dietary patterns and breast cancer risk (15).

Furthermore, the World Cancer Research Fund also reported that no statistically significant association was found between vegetables (including fruits) and breast cancer (36). However, a study examining Singapore Chinese women demonstrated that there was a dose-dependent trend of decreasing breast cancer risk for the vegetable-fruit-soy dietary pattern only among postmenopausal women (14).

Kimchi is a traditional Korean food manufactured by fermenting vegetables with probiotic lactic acid bacteria. Kimchi can be considered a vegetable probiotic food that contributes health benefits in a similar manner as yogurt as a dairy probiotic food (37). Cancer preventive/anticarcinogenic activity of kimchi is associated with the type of ingredients and products formed during fermentation (38). Thoennissen et al. (39) demonstrated that capsaicin caused cell-cycle arrest and apoptosis in breast cancer cells by modulating the epidermal growth factor receptor/human epidermal growth factor receptor 2 pathway and inhibited the development of pre-neoplastic breast lesions by up to 80% without toxicity.

However, in the present study, we found there was no dose-dependent trend of breast cancer risk among Korean dietary patterns. Diversities exist among cooking methods or types of vegetables among each

country, which may account for the differences observed between the various studies. The major strengths of our study include its large sample size and prospective design, in which information was collected before the diagnosis of breast cancer, eliminating the potential recall bias that occur in case-control studies. In addition, we retrieved cancer diagnosis data that had high sensitivity and completeness from the Korean Central Cancer Registry. Our study has some limitations. First, breast cancer is a heterogeneous disease, and several studies have suggested that risk factors for breast cancer may differ in their association depending on tumor receptor status (13, 14). Nevertheless, we were unable to consider the hormone receptor status since we had no data on the participants' molecular subtype. Second, we used a shorter version of the FFQ at baseline, such that we could not consider the possibility that secular transitions in dietary patterns may have occurred during follow-up. Third, we could not exclude the possibility of errors in measuring dietary intake. The diet assessment tool included a limited number of food items, although the tool was validated and the correlation with 3-day diet records confirmed. Fourth, the number of participants in this cohort is relatively large, nevertheless, the number of breast cancer cases was limited in the final analysis (only 135 incident breast cancers). In addition, of 67,271 female cohort member with data collection from 2004–2013, a very large proportion (78%) had missing dietary data although the distributions of general characteristics did not differ between study participants with dietary data and without dietary data (Supplementary Table 2).

Our study found that a new dietary pattern, characterized by high consumption of eggs, oil, dairy products, fruits, and bread, was associated with an increased risk of breast cancer among pre-menopausal women. In contrast, the Korean and sweet dietary patterns were not associated with breast cancer risk. Large scale prospective studies in Asian women are needed to confirm our findings.

Ethics Committee Approval: The Yonsei University Health System Institutional Review Board approved the study (decision no: Y-2020-0142, date: 05.10.2020).

Informed Consent: All participants provided written, informed consent prior to participation.

Authorship Contributions

Concept: J.Y.L., H.I.C., H.K.; Design: J.Y.L., H.I.C., H.K.; Data Collection and/or Processing: J.Y.L., H.I.C., H.K.; Analysis and/or Interpretation: J.Y.L., H.I.C., H.K.; Literature Search: J.Y.L., H.I.C., H.K.; Writing: J.Y.L., H.I.C., H.K.

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

Financial Disclosure: The present research has been supported by the Korea Breast Cancer Foundation.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136: E359-E386. (PMID: 25220842) [Crossref]
2. Hong S, Won YJ, Lee JJ, Jung KW, Kong HJ, Im JS, et al. Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2018. Cancer Res Treat. 2021; 53: 301-315. (PMID: 33735559) [Crossref]
3. Michels KB, Mohllajee AP, Roset-Bahmanyar E, Beehler GP, Moysich KB. Diet and breast cancer: a review of the prospective observational studies. Cancer. 2007; 109(12 Suppl): 2712-2749. (PMID: 17503428) [Crossref]
4. Clinton SK, Giovannucci EL, Hursting SD. The World Cancer Research Fund/American Institute for Cancer Research Third Expert Report on Diet, Nutrition, Physical Activity, and Cancer: Impact and Future Directions. J Nutr. 2020; 150: 663-671. (PMID:31758189) [Crossref]
5. Martin LJ, Li Q, Melnichouk O, Greenberg C, Minkin S, Hislop G, et al. A randomized trial of dietary intervention for breast cancer prevention. Cancer Res. 2011; 71: 123-133. (PMID: 21199800) [Crossref]
6. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA. 2006; 295: 629-642. (PMID: 16467232) [Crossref]
7. Kant AK. Dietary patterns and health outcomes. J Am Diet Assoc. 2004; 104: 615-635. (PMID: 15054348) [Crossref]
8. Edefonti V, Randi G, La Vecchia C, Ferraroni M, Decarli A. Dietary patterns and breast cancer: a review with focus on methodological issues. Nutr Rev. 2009; 67: 297-314. (PMID: 19519672) [Crossref]
9. Fung TT, Hu FB, Holmes MD, Rosner BA, Hunter DJ, Colditz GA, et al. Dietary patterns and the risk of postmenopausal breast cancer. Int J Cancer. 2005; 116: 116-121. (PMID: 15756679) [Crossref]
10. Guinter MA, McLain AC, Merchant AT, Sandler DP, Steck SE. A dietary pattern based on estrogen metabolism is associated with breast cancer risk in a prospective cohort of postmenopausal women. Int J Cancer. 2018; 143: 580-590. (PMID: 29574860) [Crossref]
11. Link LB, Canchola AJ, Bernstein L, Clarke CA, Stram DO, Ursin G, et al. Dietary patterns and breast cancer risk in the California Teachers Study cohort. Am J Clin Nutr. 2013; 98: 1524-1532. (PMID: 24108781) [Crossref]
12. Pot GK, Stephen AM, Dahm CC, Key TJ, Cairns BJ, Burley VJ, et al. Dietary patterns derived with multiple methods from food diaries and breast cancer risk in the UK Dietary Cohort Consortium. Eur J Clin Nutr. 2014; 68: 1353-1358. (PMID: 25052230) [Crossref]
13. Velie EM, Schairer C, Flood A, He JP, Khattree R, Schatzkin A. Empirically derived dietary patterns and risk of postmenopausal breast cancer in a large prospective cohort study. Am J Clin Nutr. 2005; 82: 1308-1319. (PMID: 16332665) [Crossref]
14. Butler LM, Wu AH, Wang R, Koh WP, Yuan JM, Yu MC. A vegetable-fruit-soy dietary pattern protects against breast cancer among postmenopausal Singapore Chinese women. Am J Clin Nutr. 2010; 91: 1013-1019. (PMID: 20181808) [Crossref]
15. Kojima R, Okada E, Ukawa S, Mori M, Wakai K, Date C, et al. Dietary patterns and breast cancer risk in a prospective Japanese study. Breast Cancer. 2017; 24: 152-160. (PMID: 26993124) [Crossref]
16. Zhang CX, Ho SC, Fu JH, Cheng SZ, Chen YM, Lin FY. Dietary patterns and breast cancer risk among Chinese women. Cancer Cause Control. 2011; 22: 115-124. (PMID: 21080051) [Crossref]
17. Cui X, Dai Q, Tseng M, Shu XO, Gao YT, Zheng W. Dietary patterns and breast cancer risk in the shanghai breast cancer study. Cancer Epidemiol Biomarkers Prev. 2007; 16: 1443-1448. (PMID: 17623805) [Crossref]
18. Jee YH, Emberson J, Jung KJ, Lee SJ, Lee S, Back JH, et al. Cohort Profile: The Korean Cancer Prevention Study-II (KCPS-II) Biobank. Int J Epidemiol. 2018; 47: 385-386f. (PMID: 29186422) [Crossref]
19. Lim H, Kim SY, Wang Y, Lee SJ, Oh K, Sohn CY, et al. Preservation of a traditional Korean dietary pattern and emergence of a fruit and dairy dietary pattern among adults in South Korea: secular transitions in dietary patterns of a prospective study from 1998 to 2010. Nutr Res. 2014; 34: 760-770. (PMID: 25262419) [Crossref]

20. Thompson FE, Byers T. Dietary assessment resource manual. J Nutr. 1994; 124(11 Suppl): 2245S-2317S. (PMID: 7965210) [Crossref]
21. Adebamowo CA, Hu FB, Cho E, Spiegelman D, Holmes MD, Willett WC. Dietary patterns and the risk of breast cancer. Ann Epidemiol. 2005; 15: 789-795. (PMID: 16257363) [Crossref]
22. Agurs-Collins T, Rosenberg L, Makambi K, Palmer JR, Adams-Campbell L. Dietary patterns and breast cancer risk in women participating in the Black Women's Health Study. Am J Clin Nutr. 2009; 90: 621-628. (PMID: 19587089) [Crossref]
23. Xiao Y, Xia J, Li L, Ke Y, Cheng J, Xie Y, et al. Associations between dietary patterns and the risk of breast cancer: a systematic review and meta-analysis of observational studies. Breast Cancer Res. 2019; 21: 16. (PMID: 30696460) [Crossref]
24. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002; 13: 3-9. (PMID: 11790957) [Crossref]
25. Kweon S, Kim Y, Jang MJ, Kim Y, Kim K, Choi S, et al. Data resource profile: the Korea National Health and Nutrition Examination Survey (KNHANES). Int J Epidemiol. 2014; 43: 69-77. (PMID: 24585853) [Crossref]
26. Albuquerque RC, Baltar VT, Marchioni DM. Breast cancer and dietary patterns: a systematic review. Nutr Rev. 2014; 72: 1-17. (PMID: 24330083) [Crossref]
27. Brennan SF, Cantwell MM, Cardwell CR, Velentzis LS, Woodside JV. Dietary patterns and breast cancer risk: a systematic review and meta-analysis. Am J Clin Nutr. 2010; 91: 1294-1302. (PMID: 20219961) [Crossref]
28. Jun S, Ha K, Chung S, Joung H. Meat and milk intake in the rice-based Korean diet: impact on cancer and metabolic syndrome. Proc Nutr Soc. 2016; 75: 374-384. (PMID: 26975473) [Crossref]
29. Catsburg C, Kim RS, Kirsh VA, Soskolne CL, Kreiger N, Rohan TE: Dietary patterns and breast cancer risk: a study in 2 cohorts. Am J Clin Nutr. 2015; 101: 817-823. (PMID: 25833979) [Crossref]
30. Ziegler RG, Hoover RN, Pike MC, Hildesheim A, Nomura AM, West DW, et al. Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst. 1993; 85: 1819-1827. (PMID: 8230262) [Crossref]
31. Kaklamani VG, Linos A, Kaklamani E, Markaki I, Koumantaki Y, Mantzoros CS. Dietary fat and carbohydrates are independently associated with circulating insulin-like growth factor 1 and insulin-like growth factor-binding protein 3 concentrations in healthy adults. J Clin Oncol. 1999; 17: 3291-3298. (PMID: 10506632) [Crossref]
32. Forman MR. Changes in dietary fat and fiber and serum hormone concentrations: nutritional strategies for breast cancer prevention over the life course. J Nutr. 2007; 137(1 Suppl): 170S-174S. (PMID: 17182821) [Crossref]
33. Jung S, Goloubeva O, Klifa C, LeBlanc ES, Snetselaar LG, Van Horn L, et al. Dietary Fat Intake During Adolescence and Breast Density Among Young Women. Cancer Epidemiol Biomarkers Prev. 2016; 25: 918-926. [Crossref]
34. Willett WC. Diet and breast cancer. J Intern Med. 2001; 249: 395-411. (PMID: 11350564) [Crossref]
35. Suzuki R, Iwasaki M, Hara A, Inoue M, Sasazuki S, Sawada N, et al. Fruit and vegetable intake and breast cancer risk defined by estrogen and progesterone receptor status: the Japan Public Health Center-based Prospective Study. Cancer Cause Control. 2013; 24: 2117-2128. (PMID: 24091793) [Crossref]
36. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: A global perspective. Proc Nutr Soc. 2008; 67: 253-256. (PMID: 18452640) [Crossref]
37. Park KY, Jeong JK, Lee YE, Daily JW 3rd. Health benefits of kimchi (Korean fermented vegetables) as a probiotic food. J Med Food. 2014; 17: 6-20. (PMID: 24456350) [Crossref]
38. Park KY, Cho EJ, Rhee SH. Increased antimutagenic and anticancer activities of Chinese cabbage by changing kinds and levels of sub-ingredient. J Korean Soc Food Sci Nutr. 1998, 27: 625-632. [Crossref]
39. Thoennissen NH, O'Kelly J, Lu D, Iwanski GB, La DT, Abbassi S, et al. Capsaicin causes cell-cycle arrest and apoptosis in ER-positive and -negative breast cancer cells by modulating the EGFR/HER-2 pathway. Oncogene. 2010; 29: 285-296. [Crossref]

Supplementary Table 1. Food items and food groups for dietary pattern analysis

No	Food items	Foods or food groups
Korean dietary pattern		
1	Fishes, processed meats, tofu, bean products	Meats, fishes, tofu
2	Herbs and vegetables	Herbs and vegetables
3	Kimchi (Korean cabbage)	Kimchi
4	Cooked rice, bread, cooked noodles	Rice, bread, noodles
5	Potatoes, sweet potatoes	Potatoes and sweet potatoes
Sweet dietary pattern		
6	Sugar, honey	Sugar and honey
7	Sugar on coffee or tea	Sugar and honey
8	Jam, honey	Sugar and honey
9	Coke, carbonated beverage	Soda
New (Western-like) dietary pattern		
10	Eggs	Eggs
11	Egg type (scramble eggs, fried eggs, scrolled eggs)	Oil
12	Milk	Milk and dairy products
13	Yogurt, ice cream, cheese, other products	Milk and dairy products
14	Bread and snacks	Bread and snacks
15	Butter, margarine	Oil
16	Mayonnaise dressing food, fried food, stir-fried food	Oil
17	Fruits	Fruits

Supplementary Table 2. General characteristics of study participants stratified by with and without dietary data

	Participants with diet data (*n* = 14,807)	**Participants without diet data (*n* = 52,464)**	**Total participants (*n* = 67,271)**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Age, year	46.39 (11.04)	39.93 (11.03)	41.35 (11.36)
Body mass index, kg/m^2	23.04 (3.09)	22.09 (3.12)	22.30 (3.14)
Smoking status			
Never	13461 (90.81)	46010 (87.60)	59471 (88.31)
Ex	680 (4.59)	4430 (8.43)	5110 (7.59)
Current	682 (4.60)	2080 (3.96)	2762 (4.10)
Exercise			
Yes	7383 (50.03)	24388 (46.65)	31771 (47.39)
No	7375 (49.97)	27890 (53.35)	35265 (52.61)
Alcohol drinking			
Never	8494 (57.30)	15961 (30.39)	24455 (36.31)
Ex	561 (3.78)	9233 (17.58)	9794 (14.54)
Current	5768 (38.91)	27326 (52.03)	33094 (49.14)

SD: Standard deviation

Original Article

Eur J Breast Health 2024; 20(4): 270-276
DOI: 10.4274/ejbh.galenos.2024.2024-5-11

Applying the SOUND Trial for Omitting Axillary Surgery in Patients With Early Breast Cancer in Bahrain

Ali Hasan Abdulla[1], Reem Althawadi[1], Ahmed Zuhair Salman[1], Tareq Hamed Altaei[2], Amina Mohamed Mahdi[2], Hussain Adnan Abdulla[1]

[1]Department of Surgery, Salmaniya Medical Complex, Government Hospitals, Manama, Bahrain
[2]Department of Radiology, Salmaniya Medical Complex, Government Hospitals, Manama, Bahrain

ABSTRACT

Objective: The Sentinel Node vs. Observation After Axillary Ultra-Sound (SOUND) trial reported that omission of axillary surgery was not inferior to sentinel lymph node biopsy (SLNB) in those with cT1 breast cancer and negative preoperative axillary ultrasound. The aim of our study was to evaluate the clinical characteristics of early breast cancer patients undergoing breast conserving surgery (BCS) at our institution in order to investigate the exportability of SOUND criteria to our patient population.

Materials and Methods: We retrospectively reviewed patients with cT1N0 breast cancer undergoing BCS and adjuvant radiotherapy according to the SOUND trial criteria. Comparison was made between the eligible group of our cohort and the SLNB arm of the SOUND trial.

Results: The proportion of younger patients was higher in our eligible cohort (37.7% *vs.* 17.5%, $p = 0.002$). Postmenopausal patients were more prevalent in the SOUND trial (79.4% *vs.* 56.6%, $p = 0.004$). On final pathology, tumours were more likely to be upgraded to T2 in our group (26.4% vs. 4.4%, $p = 0.001$). Patients in our cohort were more likely to receive adjuvant chemotherapy (37.7% *vs.* 20.1%, $p = 0.002$).

Conclusion: The clinicopathological differences between our cohort and the SOUND trial population could be attributed to aggressive tumours in Bahrain compared to Western countries. Our study may influence others to investigate the applicability of the SOUND trial in clinical practice. Nevertheless, it is a study that should generate multidisciplinary discussion in the de-escalation of axillary surgery.

Keywords: Early breast cancer; sentinel lymph node biopsy; axillary surgery; breast conserving surgery; SOUND trial

Cite this article as: Abdulla AH, Althawadi R, Salman AZ, Altaei TH, Mahdi AM, Abdulla HA. Applying the SOUND Trial for Omitting Axillary Surgery in Patients With Early Breast Cancer in Bahrain. Eur J Breast Health. 2024; 20(4): 270-276

Key Points

- Sentinel lymph node biopsy (SLNB) is the standard of care in clinically node-negative breast cancer for axillary staging and locoregional control.
- The Sentinel Node vs. Observation After Axillary Ultra-Sound (SOUND) trial concluded that patients with small breast cancer and sonographically normal appearing lymph nodes can be safely spared any axillary surgery, as lack of pathological information does not influence adjuvant therapy.
- Compared to the SOUND trial, early breast cancer patients in Bahrain tend to be of younger age, premenopausal, have larger tumours on final pathology and are more likely to receive adjuvant chemotherapy.
- Given the difference between our population and the SOUND trial patients, our findings still support a role for SLNB to guide adjuvant therapy decisions.
- This study evaluates the applicability of the SOUND trial in a real-world patient population.

Introduction

The management of the axilla in breast cancer has changed considerably in the past few decades. In early breast cancer, sentinel lymph node biopsy (SLNB) has replaced axillary dissection as the standard of care for axillary staging and locoregional control (1, 2). The landmark American College of Surgeons Oncology Group Z0011 (ACOSOG Z0011) trial (3) has revolutionised axillary management in women undergoing breast conserving surgery (BCS) followed by adjuvant radiotherapy and systemic therapy, sparing patients axillary dissection even when 1–2 sentinel nodes are positive for macrometastasis. The findings from the ACOSOG Z0011 trial were supported by other randomised controlled trials and became the standard for axillary management in early breast cancer, showing reduced patient morbidity without compromised oncological outcomes (4, 5). Despite presentation of ACOSOG Z0011 data in 2010, the trial was debated and has not yet been incorporated into practice (6). It was only between 2016 and 2017 when we started to adopt the ACOSOG Z0011 criteria in Bahrain, after an updated clinical practice guideline was recommended by

Corresponding Author:
Hussain Adnan Abdulla; hussainaabdulla@yahoo.com

Received: 28.05.2024
Accepted: 27.07.2024
Available Online Date: 26.09.2024

the National Comprehensive Cancer Network (7), representing a milestone in surgical de-escalation.

There are several prospective randomised trials evaluating the omission of SLNB in clinically node-negative early breast cancer patients undergoing upfront surgery (8). The Sentinel Node vs. Observation After Axillary Ultra-Sound (SOUND) trial (9) was the earliest to open in 2012 and it was published recently. It reported that omission of axillary surgery was not inferior to SLNB in those with cT1 breast cancer and negative preoperative axillary ultrasound, meaning that these patients can be safely spared axillary surgery when the lack of pathological nodal status does not influence the adjuvant treatment decisions (10). They found no difference in baseline characteristics, in five-year distant disease-free survival and the rate of axillary recurrences between those that underwent SLNB and patients that did not. Although this trial is unlikely to change clinical practice immediately, it is a study that will likely influence multidisciplinary discussion. The aim of this study was to review the clinical characteristics of early breast cancer patients undergoing BCS and SLNB in Bahrain at a single centre in order to evaluate the external generalisability of SOUND criteria to our patient population.

Materials and Methods

This study was approved by the Ethical Committee of Government Hospitals Bahrain (approval number: 116051223, date: 05.12.2023). We conducted a retrospective review from a prospectively maintained database, from October 2021 to September 2023. Patients were included if they had cT1-T2 breast cancer without palpable adenopathy before surgery, underwent SLNB with no prior neoadjuvant systemic therapy. Patients were excluded if they had failure of localisation of sentinel lymph nodes, multiple suspicious lymph nodes, extensive multifocality or multicentricity, bilateral cancers, those with local recurrence and synchronous tumours. The recruited patients were then divided into two groups according to the SOUND trial criteria: Women with invasive breast cancer up to 2 cm in diameter, no axillary lymphadenopathy at clinical evaluation and a plan to undergo BCS and adjuvant radiotherapy. The eligible group comprised patients who met the SOUND trial criteria for omitting axillary surgery, while the ineligible group consisted of patients who did not meet these criteria.

All patients underwent bilateral mammogram and ultrasound of breasts and axillae to define the clinical T and N stage. In case of a suspicious lymph node on ultrasound, a biopsy was performed to rule out the presence of nodal metastases. Patients were excluded if the biopsy confirmed axillary metastasis. At our institution, we do not proceed with SLNB for patients with 1–2 suspicious lymph nodes on ultrasound, due to demand by our oncologists and the tumour board for comprehensive investigation, including axillary biopsy. Patients with a biopsy positive for axillary metastasis undergo upfront axillary dissection or neoadjuvant therapy, and these patients were excluded from the study. All patients with clinically node-negative invasive cancer or a node biopsy negative for metastasis had SLNB to stage the axilla. SLNB was performed using dual technique, comprising radioisotope and patent blue dye. Intraoperative frozen section was carried out in all patients. Completion axillary lymph node dissection (ALND) was performed if >2 nodes contained macrometastases, applying ACOSOG Z0011 criteria.

Statistical Analysis

The following patient demographics and tumour characteristics were collected and tabulated: age at diagnosis, menopausal status, histological tumour type, tumour grade, pathological tumour size, pathological nodal status, oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2) status, Ki-67 index, tumour molecular subtype and type of adjuvant therapy received. The eligible group was compared with the ineligible group. Comparison was then made between the eligible group of our cohort and the SLNB arm of the SOUND trial using the chi-squared test. Statistical analysis was performed using SPSS software, version 29.0 (IBM, Armonk, NY, USA). *P*-values less than 0.05 were considered to be significant.

Results

A total of 147 patients with early breast cancer underwent SLNB at our institution between October 2021 and September 2023. Baseline characteristics of the study population are summarised in Table 1. All patients were female. The median (range) number of sentinel nodes removed was 3 (1–5), while the median number of histologically pathological sentinel nodes was 2 (1–4). Approximately one-quarter of patients had macrometastases (23.1%), with only 5.4% of cases undergoing axillary dissection. Out of the 147 patients, only 53 patients who met the SOUND criteria for omitting SLNB were included in the eligible group, while 94 patients who did not meet the criteria were labelled as ineligible and excluded from the analysis, having cT2 tumours or a mastectomy (Figure 1).

Table 2 compares the eligible patients in our study and those in the SOUND trial SLNB arm. The factors showing significant differences between the two groups were age, menopausal status, tumour size on final pathology and adjuvant chemotherapy. In particular, even though the majority of patients in both cohorts were 50 years or older, the proportion of younger (<50 years) patients in our eligible group was approximately twice a large than that in the SOUND trial (37.7% *vs.* 17.5%, $p = 0.002$). Similarly, a higher percentage of premenopausal patients were observed in our eligible group compared with the no axillary surgery arm in the SOUND trial (43.4% *vs.* 20.6%, $p = 0.004$). On final pathology, over a quarter of our patients were upgraded to T2 tumours, compared to only 4.4% in the SOUND trial cohort ($p = 0.001$). The patients in our eligible group were more likely to receive adjuvant chemotherapy than those in the SOUND trial population (37.7% *vs.* 20.1%, $p = 0.002$). Otherwise, there were no significant differences between the two cohorts in terms of histological subtype, tumour grade, pathological nodal status, hormone receptor

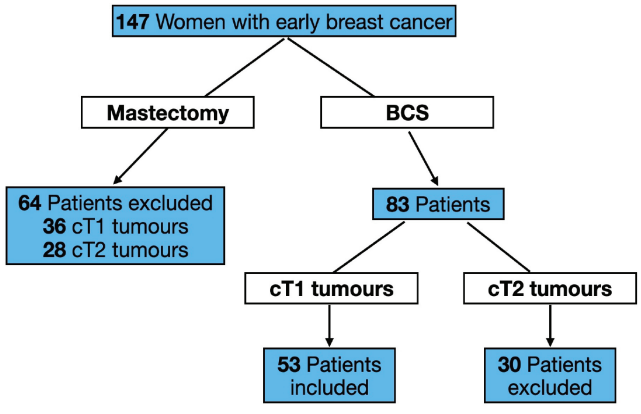

Figure 1. Flow chart representing inclusion of patients in the study analysis

BCS: Breast conserving surgery

Table 1. Clinicopathological characteristics of early breast cancer patients undergoing SLNB at our institution

Age	
Mean	56.3 (±12.3)
Median	57
Range	26–92
Menopausal status	
Premenopausal	54 (36.7%)
Postmenopausal	93 (63.3%)
Histology	
Ductal	121 (82.3%)
Lobular	16 (10.9%)
Other	10 (6.8%)
cT stage	
T1mi or T1a	2 (1.36%)
T1b	18 (12.2%)
T1c	69 (46.9%)
T2	58 (39.4%)
pT stage	
T1mi or T1a	10 (6.8%)
T1b	17 (11.6%)
T1c	50 (34.0%)
T2	70 (47.6%)
pN status	
N0	108 (73.4%)
N1mi	5 (3.4%)
N1	29 (19.7%)
N2	5 (3.4%)
Tumor grade	
1	34 (23.1%)
2	91 (61.9%)
3	22 (14.9%)
ER status	
Negative	133 (90.5%)
Positive	14 (9.5%)
PR status	
Negative	121 (82.3%)
Positive	26 (17.6%)
HER2 status	
Positive	14 (9.5%)
Negative	133 (90.5%)
Ki-67 index	
<20	91(61.9%)
≥20	56 (38.1%)
Hormonal therapy	
Yes	132 (89.8%)
No	15 (10.2%)
Chemotherapy	
No	45 (30.6%)
Yes	102 (69.4%)
Radiotherapy	
Yes	104 (70.7%)
No	43 (29.3%)
Trastuzumab	
Yes	14 (9.5%)
No	133 (90.5%)
Surgery	
Breast conserving surgery	83 (56.5%)
Mastectomy	64 (43.5%)

SLNB: Sentinel lymph node biopsy; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2

and HER2 status, Ki-67 proliferation index and other modalities of adjuvant therapies.

Discussion and Conclusion

The present study retrospectively evaluated feasibility of applying the SOUND trial strategy for omission of SLNB to a cohort of breast cancer patients in Bahrain. To the best of our knowledge, this is the first study in literature investigating the exportability of SOUND trial findings to avoid axillary surgery in other breast cancer populations.

Our results demonstrate some differences between our group of patients who were potentially eligible for omitting SLNB according to the SOUND criteria and the SLNB population in the SOUND trial. Of note, the percentages of younger and premenopausal patients in our study were significantly higher than those of patients in the SOUND trial. This difference could be related to social, economic and population differences in the age of diagnosis between Arab and Western populations (11). Another explanation could be attributed to the fact that Arab countries generally have a younger population compared to Western countries (12). This reflects the relatively higher proportion of breast cancer patients in Bahrain with more aggressive disease compared to Western populations (11). Specifically, our patients tend to be of younger age and have larger and higher grade tumours, and these are likely to be risk factors for the significant proportion of axillary lymph node metastasis in Bahrain (13). There was a higher proportion of pathological T2 tumours in our eligible group compared with the SOUND cohort. This could be linked to underestimation of tumour size by preoperative imaging, as ultrasound and mammogram have been reported to underestimate the size of clinically T1 tumours (up to 20 mm) (14), with radiological and pathological concordance influenced by various factors, including tumour histology, molecular subtypes and breast density (15).

Data from the SOUND trial indicated that adjuvant treatments were not significantly different between the SLNB group and the no axillary surgery group (10). However, a relatively higher percentage of patients who underwent adjuvant chemotherapy were observed in our cohort compared to those in the SOUND trial, indicating the

Table 2. Comparison of patients in the current study and the SLNB arm in the SOUND trial

	Patients, No. (%)		
Characteristic	**Current study (*n* = 53)**	**SOUND trial (*n* = 708)**	***p*-value**
Age			
<50	20 (37.7)	124 (17.5)	0.002
≥50	33 (62.3)	584 (82.5)	
Menopausal status			
Premenopausal	23 (43.4)	145 (20.6)	0.004
Postmenopausal	30 (56.6)	558 (79.4)	
Histology			
Ductal	45 (84.9)	551 (77.8)	0.419
Lobular	4 (7.5)	61 (8.6)	
Other	4 (7.5)	96 (13.5)	
pT stage			
T1mi or T1a	4 (7.5)	71 (10.0)	
T1b	10 (18.9)	251 (35.5)	0.001
T1c	25 (47.2)	355 (50.1)	
T2	14 (26.4)	31 (4.4)	
pN status			
Nx	0	12 (1.7)	
N0 or N0 (i+)	42 (79.2)	599 (84.6)	0.098
N1mi	2 (3.8)	36 (5.1)	
N1	8 (15.1)	57 (8.1)	
N2	1 (1.9)	4 (0.6)	
Tumor grade			
1	10 (18.9)	194 (27.7)	0.233
2	32 (60.3)	377 (53.8)	
3	11 (20.8)	130 (18.5)	
ER status			
Negative	6 (11.3)	56 (7.9)	0.158
Positive	47 (88.7)	652 (92.1)	
PR status			
Negative	11 (20.8)	108 (15.3)	0.151
Positive	42 (79.2)	600 (84.7)	
Ki-67 index			
<20	29 (54.7)	455 (64.4)	0.220
≥20	24 (45.3)	252 (35.6)	
HER2 status			
Negative	47 (88.7)	660 (93.2)	0.096
Positive	6 (11.3)	48 (6.8)	
Molecular subtype			
Luminal HER2-negative	44 (83)	617 (87.1)	0.423
HER2-enriched	6 (11.3)	48 (6.8)	
Triple-negative	3 (5.7)	33 (6.1)	

Table 2. Continued

	Patients, No. (%)		
Characteristic	**Current study (*n* = 53)**	**SOUND trial (*n* = 708)**	***p*-value**
Hormonal therapy			
No	6 (11.3)	66 (9.3)	0.248
Yes	47 (88.7)	642 (90.7)	
Chemotherapy			
No	33 (62.3)	566 (79.9)	0.002
Yes	20 (37.7)	142 (20.1)	
Radiotherapy			
No	2 (3.7)	14 (2.0)	0.551
Yes	51 (96.3)	694 (98.0)	
Trastuzumab			
No	47 (88.7)	661 (93.4)	0.192
Yes	6 (11.3)	47 (6.6)	

SLNB: Sentinel lymph node biopsy; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2; SOUND: The Sentinel Node vs. Observation After Axillary Ultra-Sound

SLNB still has a role in Bahraini patients for axillary staging in order to guide adjuvant therapy decisions. As outlined in the RxPONDER (A Clinical Trial RX for Positive Node, Endocrine Responsive Breast Cancer) trial, chemotherapy is associated with a survival benefit in younger patients with node-positive disease (16). Furthermore, identification of nodal disease in ER-positive breast cancer influences treatment options in terms of cyclin-dependent kinase 4 and 6 inhibitor eligibility as well as extended hormonal therapy (up to 10 years) (17-19). In addition, the absence of pathological nodal disease may allow for de-escalation of hormonal therapy, both in terms of choice of medication and duration of treatment (10). On the other hand, in patients with other molecular tumour subtypes undergoing upfront surgery, nodal status might be important to properly tailor adjuvant systemic therapy. In particular, adjuvant treatment in node-negative patients with HER2-positive disease might only be limited to paclitaxel and trastuzumab (20).

The data from the SOUND trial support the Society of Surgical Oncology Choosing Wisely guideline recommendation against routine SLNB in patients aged over 70 years with small hormone receptor-positive and HER2-negative breast cancer, as axillary surgery does not influence adjuvant therapy decisions in these patients (21). A previous study from our institution also reported findings consistent with the Choosing Wisely campaign, suggesting the safety of omitting SLNB in this subset of patients (13). In terms of adjuvant radiation therapy, nodal radiation fields are usually included for patients with nodal involvement as a complement to whole-breast radiation after BCS (10). On the contrary, select patients aged 65 years and older with node-negative disease would be candidates for omission of radiation therapy (22).

The findings from the SOUND trial evaluated the reliability of ultrasound to detect nodal involvement and implied whether it might replace axillary surgery for staging in the future (23). The sensitivity of axillary ultrasound to detect lymph node involvement ranges from 24–94% (24). Although the presence of axillary metastases was relatively higher in our group compared to that of the SOUND trial (20.8% *vs.* 15.9%), the difference was not statistically significant. Given the very limited number of patients with extensive nodal involvement in our group (1.9%) and the extremely low incidence of axillary recurrence in the no axillary surgery group of the SOUND trial (0.4% at 5 years), the use of ultrasound can be clinically meaningful to rule out nodal involvement (10). Even though the SOUND trial is unlikely to be incorporated into the guidelines immediately, multidisciplinary discussions are important before applying changes in clinical practice while we look forward to future data from other trials, including the Intergroup Sentinel Mamma trial, similarly investigating omission of axillary surgery in patients with tumours up to 5 cm undergoing BCS (25).

The SOUND trial is limited by enrolment of a cohort comprising of low-risk patients, including older women and those with very small tumours, which might not be representative of real-world data. In addition, the SOUND trial, which mandated ALND for a positive sentinel node, was ongoing at the time ACOSOG Z0011 was published, when the same patients with low axillary disease burden could omit ALND. This further confirms the selection bias in the SOUND trial. Limitations of our study include its retrospective nature and small sample size. There is probable selection bias for included patients with good prognosis, as we applied a very strict criteria for performing SLNB. With lack of data on recurrence, mortality and follow-up from our cohort, there might be cases that have loco-regional recurrence and long-term follow-up is needed to confirm the validity of our data. Despite these limitations, to the best of our knowledge, this is the first published study evaluating the SOUND trial criteria in Bahraini patients with early breast cancer.

Before applying the SOUND trial to clinical practice, it is important to determine whether the trial population is representative of a real-world patient population. This study did not demonstrate external generalisability of the SOUND trial criteria to Bahraini patients with early breast cancer undergoing BCS. The differences could

be attributed to aggressive tumour characteristics in our patients compared to Western groups. Nevertheless, the SOUND trial is a landmark study in the de-escalation of axillary surgery that will influence multidisciplinary discussion. Axillary ultrasound and the use of genomic assays may obviate the need for axillary surgery to inform adjuvant systemic therapy decisions in cT1-2N0 patients with breast cancer in the future. Our study may influence other researchers to investigate the applicability of SOUND criteria to their own populations and ensure how to implement these data into their local guidelines and clinical practice.

Ethics Committee Approval: This study was approved by the Ethical Committee of Government Hospitals Bahrain (approval number: 116051223, date: 05.12.2023).

Informed Consent: We conducted a retrospective review from a prospectively maintained database, from October 2021 to September 2023.

Authorship Contributions

Surgical and Medical Practices: A.H.A., R.A., A.Z.S., T.H.A., A.M.M., H.A.A.; Concept A.M.M., H.A.A.; Design: A.M.M., H.A.A.; Data Collection and/or Processing: A.H.A., R.A., A.Z.S., T.H.A.; Analysis and/or Interpretation: A.H.A., A.Z.S., H.A.A.; Literature Search: A.H.A., R.A., A.Z.S.; Writing: A.H.A., R.A., A.Z.S., T.H.A., A.M.M., H.A.A.

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

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

References

1. Krag DN, Anderson SJ, Julian TB, Brown AN, 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]
2. Galimberti V, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013; 14: 297-305. (PMID: 23491275) [Crossref]
3. 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]
4. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJH, 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]
5. Tinterri C, Gentile D, Gatzemeier W, Sagona A, Barbieri E, Testori A, et al. Preservation of Axillary Lymph Nodes Compared with Complete Dissection in T1-2 Breast Cancer Patients Presenting One or Two Metastatic Sentinel Lymph Nodes: The SINODAR-ONE Multicenter Randomized Clinical Trial. Ann Surg Oncol. 2022; 29: 5732-5744. (PMID: 35552930) [Crossref]
6. Reimer T. Omission of axillary sentinel lymph node biopsy in early invasive breast cancer. Breast. 2023; 67: 124-128. (PMID: 36658052) [Crossref]
7. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. NCCN Guidelines Insights: Breast Cancer, Version 1.2017. J Natl Compr Canc Netw. 2017; 15: 433-451. (PMID: 28404755) [Crossref]
8. Hersh EH, King TA. De-escalating axillary surgery in early-stage breast cancer. Breast. 2022; 62: S43-S49. (PMID: 34949533) [Crossref]
9. Gentilini O, Veronesi U. Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: sentinel node vs Observation after axillary UltraSouND). Breast. 2012; 21: 678-681. (PMID: 22835916) [Crossref]
10. Gentilini OD, Botteri E, Sangalli C, Galimberti V, Porpiglia M, Agresti R, et al. Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial. JAMA Oncol. 2023; 9: 1557-1564. (PMID: 37733364) [Crossref]
11. Hamadeh RR, Abulfatih NM, Fekri MA, Al-Mehza HE. Epidemiology of Breast Cancer among Bahraini Women: Data from the Bahrain Cancer Registry. Sultan Qaboos Univ Med J. 2014; 14: e176-e182. (PMID: 24790739)
12. Najjar H, Easson A. Age at diagnosis of breast cancer in Arab nations. Int J Surg. 2010; 8: 448-452. (PMID: 20601253) [Crossref]
13. Abdulla HA, Salman AZ, Alaraibi SJ, Nazzal K, Ahmed SA, Almahari SA, et al. Risk factors associated with sentinel lymph node metastasis in clinically node-negative breast cancer. Eur J Breast Health. 2023; 19: 229-234. (PMID: 37415656) [Crossref]
14. Kapur H, Bazzarelli A, Warburton R, Pao JS, Dingee C, Chen L, et al. Accuracy of preoperative imaging estimates: opportunities to de-escalate surgery for early invasive breast cancer. Am J Surg. 2022; 24: 722-727. (PMID: 35422328) [Crossref]
15. Azhdeh S, Kaviani A, Sadighi N, Rahmani M. Accurate estimation of breast tumor size: a comprison between ultrasonography, mammography, magnetic resonance imaging, and associated contributing factors. Eur J Breast Health. 2021; 17: 53-61. (PMID: 33796831) [Crossref]
16. Kalinsky K, Barlow WE, Gralow JR, Meric-Bernstam F, Albain KS, Hayes DF, et al. 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. N Engl J Med. 2021; 385: 2336-2347. (PMID: 34914339) [Crossref]
17. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Adjuvant tamoxifen: longer against shorter (ATLAS) collaborative group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013; 381: 805-816. (PMID: 23219286) [Crossref]
18. Goss PE, Ingle JN, Pritchard KI, Robert NJ, Muss H, Gralow J, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med. 2016; 375: 209-219. (PMID: 27264120) [Crossref]
19. Johnston SRD, Toi M, O'Shaughnessy J, Rastogi P, Campone M, Neven P, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. Lancet Oncol. 2023; 24: 77-90. (PMID: 36493792) [Crossref]
20. Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med. 2015; 372: 134-141. (PMID: 25564897) [Crossref]
21. Choosing Wisely. Society of Surgical Oncology: Don't routinely use sentinel node biopsy in clinically node negative women ≥70 years of age with early stage hormone receptor positive, HER2 negative invasive breast cancer; 2019. [cited 21 January 2024] [Crossref]

22. Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in early breast cancer. N Engl J Med. 2023; 388: 585-594. (PMID: 36791159) [Crossref]

23. Gentilini OD. Lessons from the SOUND trial and future perspectives on axillary staging in breast cancer. Br J Surg. 2024; 111: znad391. (PMID: 38059555) [Crossref]

24. Le Boulc'h M, Gilhodes J, Steinmeyer Z, Molière S, Mathelin C. Pretherapeutic imaging for axillary staging in breast cancer: a systematic review and meta-analysis of ultrasonography, MRI and FDG PET. J Clin Med. 2021; 10: 1543. (PMID: 33917590) [Crossref]

25. Reimer T, Stachs A, Veselinovic K, Polata S, Müller T, Kühn T, et al. Patient-reported outcomes for the Intergroup Sentinel Mamma study (INSEMA): A randomised trial with persistent impact of axillary surgery on arm and breast symptoms in patients with early breast cancer. EClinicalMedicine. 2022; 55: 101756. (PMID: 36457648) [Crossref]

Original Article

Eur J Breast Health 2024; 20(4): 277-283
DOI: 10.4274/ejbh.galenos.2024.2024-6-3

Pathologic Complete Response After Neoadjuvant Chemotherapy in Breast Cancer Patients Treated With Mastectomy: Indications for Treatment and Oncological Outcomes

Corrado Tinterri[1,2], Shadya Sara Darwish[3], Erika Barbieri[1], Andrea Sagona[1], Valeriano Vinci[2,4], Damiano Gentile[1,2]

[1]Clinic of Breast Unit, IRCCS Humanitas Research Hospital, Milan, Italy
[2]Department of Biomedical Sciences, Humanitas University Faculty of Medicine, Milan, Italy
[3]Department of Breast Unit, Humanitas Gavazzeni Clinical Institute, Bergamo, Italy
[4]Department of Plastic and Reconstructive Surgery, Humanitas Clinical and Research Center-IRCCS, Milan, Italy

ABSTRACT

Objective: The aim of this study was to evaluate the clinical outcomes of breast cancer (BC) patients treated with neoadjuvant chemotherapy (NAC) followed by mastectomy, focusing on cases achieving pathologic complete response (pCR). The implications of residual ductal carcinoma *in situ* (DCIS) on prognosis and survival were examined.

Materials and Methods: A retrospective cohort study included BC patients treated with NAC followed by mastectomy at the breast unit of IRCCS Humanitas Research Hospital between March 2010 and October 2021. Patients were sub-grouped into two: Those with residual DCIS (ypTis) and those with complete response without residual tumor (ypT0). Key variables such as demographics, tumor characteristics, treatment regimens, and survival outcomes were analyzed.

Results: Of 681 patients treated with NAC, 175 achieved pCR, with 60 undergoing mastectomy. Among these 60 patients, 24 had residual DCIS (ypTis) while 36 had no residual invasive or *in situ* disease (ypT0). Patients with ypTis had higher rates of multifocal disease (62.5% *vs.* 27.8%, $p = 0.006$) and stage III disease (37.5% *vs.* 11.1%, $p = 0.046$). Triple-negative breast cancer was more prevalent in the ypT0 group (55.6% *vs.* 20.8%, $p = 0.005$). During a mean follow-up of 47 months, 11 patients experienced recurrence, with no significant differences in disease-free survival (DFS) and overall survival (OS) between the groups ($p = 0.781$, $p = 0.963$, respectively).

Conclusion: Residual DCIS after NAC did not significantly impact DFS or OS compared to complete pathologic response without residual DCIS. This study underscores the need for further research to refine pCR definitions and improve NAC's prognostic and therapeutic roles in BC management.

Keywords: Breast cancer; neoadjuvant chemotherapy; pathologic complete response; mastectomy; ductal carcinoma *in situ*

Cite this article as: Tinterri C, Darwish SS, Barbieri E, Sagona A, Vinci V, Gentile D. Pathologic Complete Response After Neoadjuvant Chemotherapy in Breast Cancer Patients Treated With Mastectomy: Indications for Treatment and Oncological Outcomes. Eur J Breast Health. 2024; 20(4): 277-283

Key Points

- Neoadjuvant chemotherapy (NAC) can lead to a pathologic complete response (pCR) in breast cancer (BC) patients, offering potential for better long-term outcomes.
- Among patients achieving pCR, those undergoing mastectomy were analyzed for prognosis, focusing on the presence or absence of residual ductal carcinoma *in situ* (DCIS).
- Residual DCIS (ypTis) after NAC did not significantly affect disease-free survival or overall survival compared to patients with complete pathologic response without DCIS (ypT0).
- Patients with ypTis had higher rates of multifocal disease and advanced stage III disease, whereas triple-negative BC was more prevalent in patients with ypT0.
- The presence of residual DCIS should be considered in surgical and adjuvant therapy planning, but it does not necessarily indicate a poorer prognosis.

Corresponding Author:
Damiano Gentile; damiano.gentile@humanitas.it

Received: 26.06.2024
Accepted: 31.07.2024
Available Online Date: 26.09.2024

Introduction

Breast cancer (BC) is one of the most prevalent forms of cancer affecting women worldwide. Traditionally, the standard treatment for BC involved surgery as the primary intervention, followed by adjuvant therapies. However, advances in cancer research and treatment modalities have led to the development of neoadjuvant chemotherapy (NAC), which refers to administering systemic treatment before surgery (1-3). This approach has revolutionized the management of BC and offers several advantages, including the opportunity to assess treatment response, which has been found to correlate with survival outcomes, the potential for breast-conserving surgery (BCS), and the downstaging of advanced tumors (4-7). In recent years, the concept of pathological complete response (pCR) after NAC has garnered significant attention in the field of BC treatment. The achievement of pCR has been associated with improved long-term outcomes and a higher likelihood of disease-free survival (DFS) (6, 8, 9). For this reason, many studies have focused on increasing the achievement of pCR (10, 11).

Understanding the factors associated with reaching pCR and its impact on long-term outcomes has become an area of significant interest in BC research. However, there is no single definition of pCR, as different working groups consider various aspects. Focusing on the surgical approach, mastectomy has historically been the preferred method for BC treatment. However, with the advent of neoadjuvant therapy and the growing evidence supporting the effectiveness of this treatment modality, BCS has become a viable option for patients who achieve pCR (12-14). In some selected cases, mastectomy remains the preferred approach (15-17). This is true when oncological radicality cannot be achieved with BCS, the disease burden is still high compared to the breast volume, or there is an extensive component of residual microcalcifications. In a few selected cases, mastectomy may also be performed based on the patient's preference. In the present article, we evaluated BC treated with neoadjuvant therapy, focusing specifically on cases where patients achieved pCR and were surgically treated with mastectomy. We explored the implications of achieving pCR in terms of prognosis and survival outcomes, depending on the presence or absence of the residual ductal carcinoma *in situ* (DCIS) component. In addition, we analyzed the differences between the two DCIS subgroups from a demographic and cancer-specific perspectives, aiming to explain the different outcomes and survival benefits, if present.

Materials and Methods

Study Design

A retrospective cohort study was conducted to investigate the clinical outcomes of BC patients treated with NAC followed by mastectomy, specifically focusing on cases with a pCR. The study included patients diagnosed with BC of any biological subtype who underwent NAC and subsequent mastectomy between March 2010 and October 2021 at the breast unit of IRCCS Humanitas Research Hospital in Rozzano (Milan, Italy). Medical records of patients from a prospectively maintained institutional database were reviewed to identify eligible participants. Inclusion criteria comprised patients >18 years old, with histologically confirmed invasive BC, receipt of neoadjuvant therapy (chemotherapy, targeted therapy, or a combination), and subsequent mastectomy with a pCR on the surgical specimen. Bilateral mammography and breast ultrasound were routinely performed at the time of diagnosis, regardless of the reason leading to diagnosis, which could be part of the screening program or after symptoms onset. All patients enrolled had a histological diagnosis of invasive BC performed by an ultrasound-guided core needle biopsy, a stereotaxis-guided core needle biopsy, or a vacuum-assisted core needle biopsy, depending on tumor presentation, that is nodular or not, size, and site. Biological factors were routinely assessed. In order to complete the diagnostic process, a contrasted-enhanced bilateral magnetic resonance imaging (MRI) or contrasted-enhanced mammography were performed by highly qualified breast radiologists. In addition, a complete blood test routine, including a complete blood count, renal and liver function tests, and the CA 15-3 tumor marker, was performed. Regarding systemic staging, a chest X-ray, and a complete abdominal ultrasound were usually considered sufficient. Exceptions were made for patients with negative prognostic factors at the time of diagnosis. If one or more risk factors were present, patients underwent a total body computed tomography (CT) scan and bone scintigraphy. A fluorodeoxyglucose positron emission tomography (FDG-PET) or FDG-PET/CT was considered a II-level exam when further confirmations were required. Chemotherapy response was assessed both clinically and radiologically, repeating mammography, breast ultrasound, and magnetic resonance after the end of neoadjuvant therapy. FDG-PET was repeated if performed at the time of diagnosis. Patients received a mastectomy either because of residual microcalcifications or the absence of pre-chemotherapy proper tumor localization, through positioning of an amagnetic clip. Patients with incomplete data, previous BC treatment, and known high oncological risk status at the time of diagnosis, including the presence of oncogenic mutations or metastatic disease at presentation, were excluded from the study. Patient demographics, clinical characteristics, neoadjuvant treatment regimens, surgical details, and adequate follow-up information were collected from electronic medical records. Key variables included age, menopausal status, tumor stage and focality, hormone receptor status (estrogen receptor, progesterone receptor), human epidermal growth factor receptor 2 (HER2) status, neoadjuvant treatment regimen, duration of NAC, nodal status at all stages, surgical approach, and pCR status. Moreover, variables such as time from diagnosis to surgery, the delta of the dimension before and after chemotherapy, and the type of adjuvant therapy applied were considered.

The histopathological assessment was conducted on post-mastectomy specimens by experienced pathologists following standardized protocols. The presence or absence of invasive cancer cells in the breast and axillary lymph nodes was evaluated to determine pCR status. Patients were grouped into two subgroups for comparison: The subgroup with residual DCIS (ypTis) and the subgroup with the absence of invasive and *in situ* disease (ypT0). In our hospital, the pathological response to NAC was evaluated using the criteria proposed by Pinder et al. (18). It is important to consider that more than one definition exists. First, it is important to determine the absence of invasive disease in the surgical specimen obtained after NAC. Still, there is no consensus on whether pCR should be considered only in the mammary tissue or also in the lymph nodal tissue (19). Several systems are used to determine pCR. The standard assessment of response to solid tumors is based on the Response Evaluation Criteria in Solid Tumors (RECIST) (20). This system considers the complete response as the disappearance of all tumoral lesions and the regression of any pathological lymph nodes to <10 mm, but it is related to a clinical and radiological evaluation. From a histopathologic standpoint, several classifications have been proposed. The American Joint Committee on Cancer considers the pCR both in the breast and the regional lymph nodes as the absence of invasive carcinoma; DCIS still present

after treatment constitutes a pCR (21). Although using other specific criteria for the response assessment, the Residual Cancer Burden (RCB) system and the Sataloff classification for NAC evaluation categorize DCIS as a pCR (22, 23). Differently, the Chevallier Method and the National Surgical Adjuvant Breast and Bowel Project categorize the residual DCIS after NAC as a separate response class from a true pCR (24). Since pCR has a prognostic value, reaching a consensus about the most accurate definition and understanding of the pathological and prognostic meaning of a residual DCIS in the breast tissue after NAC is salient. For this reason, the aim of our study was to enhance the meaning of the different possible outcomes depending on the pattern of pCR, with a particular focus on distinguishing between complete response with or without a ductal *in situ* component. The Humanitas University Research Committee and Institutional Board approved this retrospective study (approval no.: EC04-06-CT34-NAC, date: 27.05.2024).

Statistical Analysis

Descriptive statistics were calculated to summarize patient demographics and clinical characteristics. The association between categorical variables was examined using the chi-square test or Fisher's exact test, as appropriate. Survival outcomes, including DFS and overall survival (OS), were estimated using a Kaplan-Meier graph, and differences between survival curves were assessed using Cox or log-rank tests, as appropriate. Subgroup analyses were performed to explore the impact of specific factors, such as hormone receptor status or HER2 status, on pCR rates and survival outcomes. All statistical analyses were performed using StataCorp STATA (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC). A p-value <0.05 was considered statistically significant.

Results

Demographic and Tumor Characteristics

During the period considered in this retrospective study, 681 patients were treated with NAC. Among these, 175 patients achieved a pCR on the surgical specimen, considering both ypT0 and ypTis. Out of these, 60 patients (34.3%) were treated with mastectomy. Only 3 (5.0%) had a confirmed DCIS component at the diagnostic core biopsy. However, after NAC, 24 patients (40.0%) had residual DCIS in the surgical specimen (ypTis), while 36 patients (60.0%) had a pCR without residual tumor (ypT0). The median (range) age for the entire cohort was 50 (31–75) years. Among the ypT0 group, the median age was 50 (31–75) years, while in the ypTis group, it was 51 (32–71) years, with no significant difference between the groups (p = 0.188). The ypTis group had a significantly higher rate of multifocal disease (62.5%) compared to the ypT0 group (27.8%) (p = 0.006). Monofocal disease was observed in 72.2% of the ypT0 group and 37.5% of the ypTis group. Menopausal status distribution was not significantly different between the groups, with 53.3% premenopausal in the entire cohort. In the ypT0 group, 47.2% were premenopausal, compared to 62.5% in the ypTis group (p = 0.245). Six patients (10.0%) overall presented with microcalcifications in pre-treatment imaging assessment. At diagnosis, 65.0% of patients had positive lymph node status (cN+), which was 63.9% in the ypT0 group and 66.7% in the ypTis group (p = 0.825). After NAC, 26.7% remained lymph node positive, with 33.3% in the ypT0 group and 16.7% in the ypTis group (p = 0.225). Disease stage was higher in the ypTis group, with 33.3% at stage III compared to 11.1% in the ypT0 group (p = 0.046). There was a significant difference in the distribution of biological factors between the two groups (p = 0.005). In the ypT0 group, 55.6% had triple-negative breast cancer (TNBC) compared to 20.8% in the ypTis group. The median reduction in tumor size (delta dimension) was 32 (12-100) mm overall, with 31 (15-100) mm in the ypT0 group and 33 (12-100) mm in the ypTis group. The median time from diagnosis to surgery was 8 (5-14) months for the entire cohort. The demographic and tumor characteristics are detailed in Table 1.

Adjuvant Therapies and Long-Term Oncological Outcomes

Table 2 shows the adjuvant therapy distribution, demonstrating homogeneous values comparing the two groups. Radiotherapy was administered to 43.3% of the total cohort, with 44.4% in the

Table 1. Demographic and tumor characteristics distribution in the general population and in the two subgroups, ypT0 and ypTis

	All patients (n = 60)	%	ypT0 (n = 36)	%	ypTis (n = 24)	%	p-value
Age: median (range)	50 (31–75)		50 (31–75)		51 (32–71)		0.188
Focality							
Unifocal	35	58.3%	26	72.2%	9	37.5%	0.006
Multifocal	25	41.7%	10	27.8%	15	62.5%	
Menopausal status							
No	32	53.3%	17	47.2%	15	62.5%	0.245
Yes	28	46.7%	19	52.8%	9	37.5%	
Nodal status pre NAC							
N0	21	35.0%	13	36.1%	8	33.3%	0.825
N+	39	65.0%	23	63.9%	16	66.7%	
Nodal status after NAC							
N0	44	73.3%	24	66.7%	20	83.3%	0.225
N+	16	26.7%	12	33.3%	4	16.7%	

Table 1. Continued

	All patients (*n* = 60)	%	ypT0 (*n* = 36)	%	ypTis (*n* = 24)	%	*p*-value
Stage							
I	3	5.0%	3	8.3%	0	0%	0.046
II	44	73.3%	29	80.6%	15	62.5%	
III	12	20.0%	4	11.1%	8	33.3%	
Biological factor status							
HR+/HER2+	11	18.3%	2	5.6%	9	37.5%	0.005
HR-/HER2+	16	26.7%	9	25.0%	7	29.2%	
HR+/HER2-	8	13.3%	5	13.9%	3	12.5%	
TNBC	25	41.7%	20	55.6%	5	20.8%	
Ki67 (*n* = 57)							
≤20%	8	13.3%	5	13.9%	3	12.5%	1.000
>20%	49	81.7%	28	77.8%	21	87.5%	
Delta dim (mm) pre/post NAC: median (range)	32 (12–100)		31 (15–100)		33 (12–100)		
Time to surgery: median (range)	8 (5–14)		8 (6–14)		8 (5–10)		

NAC: Neoadjuvant chemotherapy; HR+: Hormonal receptor positive; HR-: Hormonal receptor negative; HER2+: Human epidermal growth factor receptor 2 positive; HER2-: Human epidermal growth factor receptor 2 negative; TNBC: Triple negative breast cancer; Dim: Dimension

Table 2. Adjuvant therapies and long-term oncological outcomes in the general population and in the two subgroups, ypT0 and ypTis

	All patients (*n* = 60)	%	ypT0 (*n* = 36)	%	ypTis (*n* = 24)	%	*p*-value
Radiotherapy	26	43.3%	16	44.4%	10	41.7%	0.832
Hormonal therapy	17	28.3%	7	19.4%	10	41.7%	
Recurrence							0.061
Local	2	3.3%	1	2.8%	1	4.2%	1.000
Distant	7	11.7%	4	11.1%	3	12.5%	
Local + distant	2	3.3%	2	5.6%	0	0%	
Death							
For BC	2	90.0%	1	2.8%	1	4.2%	1.000
For other causes	3	13.3%	2	5.6%	1	4.2%	

BC: Breast cancer

ypT0 group and 41.7% in the ypTis group (p = 0.832). Hormonal therapy was given to 28.3% of the patients, with a higher percentage in the ypTis group (41.7%) compared to the ypT0 group (19.4%), approaching statistical significance (p = 0.061). Long-term oncological outcomes are also shown in Table 2. During a mean follow-up of 47 months, 11 patients experienced recurrence. In the ypT0 group, 7 patients (19.4%) had a recurrence, compared to 4 patients (16.7%) in the ypTis group (p>0.05). Recurrences included local (3.3% total, 2.8% ypT0, 4.2% ypTis), distant (11.7% total, 11.1% ypT0, 12.5% ypTis), and combined local and distant (3.3% total, 5.6% ypT0, 0% ypTis). There were two BC-related deaths (3.3% total, 2.8% ypT0, 4.2% ypTis) and three deaths from other causes (5.6% total, 5.6% ypT0, 4.2% ypTis), with no significant difference between the groups (p>0.05). No statistical difference was observed in analyzing both DFS (p = 0.781) and OS (p = 0.963) between the two groups, as shown in Figures 1 and 2, respectively.

Discussion and Conclusion

The current study focused on patients undergoing a mastectomy after NAC to analyze a more complete pathological picture of the entire breast tissue. Radiological and clinical evaluation plays a critical role at diagnosis and post-therapy assessment, despite known limitations. For example, contrast-enhanced MRI with significant background parenchymal enhancement may have limited accuracy, especially for non-mass enhancement and small-size tumors (25). Moreover, due to the increased application of BCS, post-NAC residual DCIS could be missed if not present in the surgical specimen. By assessing the whole glandular tissue after mastectomy, we ensured a complete pathological evaluation.

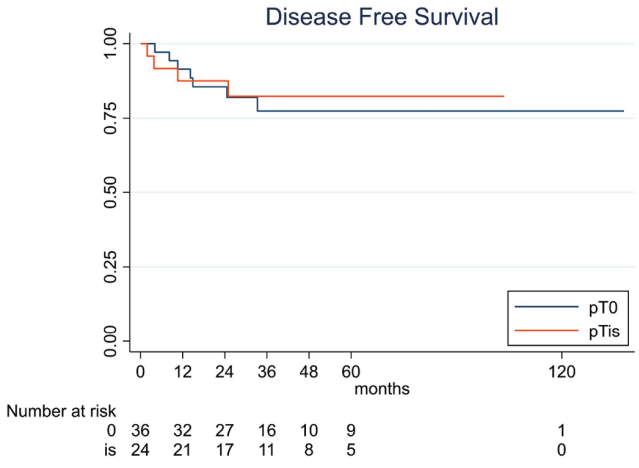

Figure 1. This figure represents the disease-free survival curves for the two groups, ypT0 and ypTis, showing no statistical difference ($p = 0.781$)

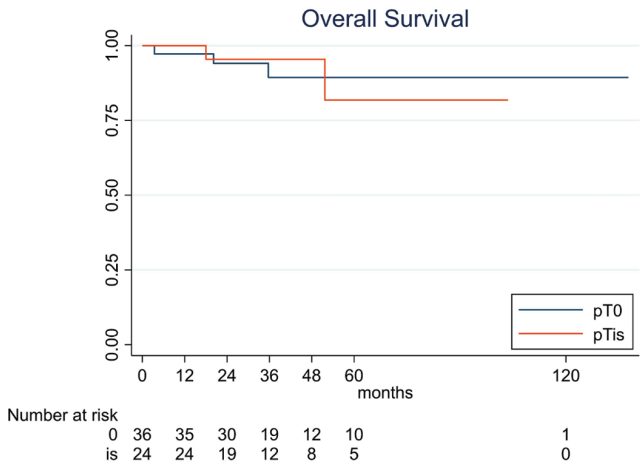

Figure 2. This figure represents the overall survival curves for the two groups, ypT0 and ypTis, showing no statistical difference ($p = 0.963$)

The reasons for performing a mastectomy were not related to the purpose of this study; data were collected retrospectively without influencing the surgical approach. Our analysis revealed that only a small percentage of patients had a DCIS component at the time of diagnosis on the core biopsy. However, a higher percentage of patients had residual DCIS in the surgical specimen. The presence of DCIS was not consistently associated with microcalcifications at diagnosis or after chemotherapy, indicating a low correlation between the two phenomena. Goldberg et al. (26) illustrated that NAC might completely eradicate DCIS while associated microcalcifications persist. A recent systematic review and meta-analysis conducted by Conforti et al. (27), found that pCR should not be used as a primary endpoint in regulatory neoadjuvant trials of BC due to weak association between pCR and long-term clinical outcomes at the trial level. This demonstrates the need for further studies to better understand the true clinical meaning of pCR without confounding factors, such as adjuvant therapies, which might alter survival outcomes (28, 29).

Currently, there is no single definition of pCR, with various classifications considering different aspects. This lack of a uniform definition creates challenges in reporting and interpreting data from neoadjuvant trials (30, 31). Some studies have shown different prognostic values for ypT0 and ypTis (32). Symmans et al. (23) calculated the RCB as a continuous index combining pathologic measurements of the primary tumor (size and cellularity) and nodal status, using corrective coefficients such as the presence of residual DCIS. The RCB was found to be a significant predictor of distant relapse-free survival (33). To address this, the Food and Drug Administration established the Collaborative Trials in Neoadjuvant Breast Cancer working group (30), which analysed data from nearly 13,000 patients enrolled in large-scale international neoadjuvant trials. They compared the three most commonly used definitions of pCR [pT0/Tis (absence of invasive cancer in the breast), pT0/Tis pN0 (absence of invasive cancer in the breast and axillary nodes), and pT0 pN0 (absence of invasive and *in situ* cancer in the breast and axillary nodes)] and their relationship to long-term patient outcome. After a pooled analysis, they recognized either pT0/Tis pN0 or pT0 pN0 for the purposes of designing trials. However, this dual definition remains an open question in BC research, which the present article sought to address.

We compared the survival outcomes between the pCR ypT0 and the pCR ypTis group to determine if a prognostic difference exists. In a meta-analysis by Broglio et al. (34), pCR in HER2+ BC was significantly associated with improved DFS and OS compared to those with residual disease. Specifically, patients achieving pCR had a hazard ratio of 0.37 for DFS and 0.34 for OS, indicating a substantially lower risk of recurrence and death. This association was more pronounced in hormone receptor-negative patients. In a retrospective study by Yoshioka et al. (35), it was found that achieving a pCR after NAC significantly improved DFS and OS in BC patients, particularly in those with high Ki67 expression. The study demonstrated that patients with TNBC, estrogen receptor-negative/HER2+, and luminal B tumors who achieved pCR had a significantly better prognosis compared to those with residual disease. However, this benefit was not observed in patients with luminal A or estrogen receptor-positive/HER2+ subtypes. However, in our study we found no differences in DFS and OS. Only a few tumor-related characteristics were statistically associated with a specific pathological response after NAC, such as TNBC, unifocal disease, and a lower stage at presentation related to a ypT0 response. Currently, no consensus has been reached concerning the prognostic value of residual DCIS after NAC. Our study demonstrated a correlation between tumor focality and stage with a ypTis response, showing that a multifocal and higher stage disease constitute a specific risk factor for residual DCIS. From a biological standpoint, luminal-like BC is mostly related to a ypTis response after NAC. These factors should be considered while planning neoadjuvant therapy for a more accurate prediction of the pathological response.

If residual DCIS after NAC does not change the prognosis, as demonstrated in this study, this knowledge should be considered during the surgical planning phase. Specifically, if only microcalcifications are present after NAC, although diffuse, a BCS could still be considered, potentially increasing the aesthetic and psychological outcomes (26). Adjuvant therapy planning could be affected by no longer considering DCIS as a residual disease to be targeted, reducing patients' exposure to unnecessary therapies in the de-escalation setting. A refined estimate of an individual's risk of recurrence, based on their subtype and RCB, might be useful for informing decisions on adjuvant treatment selection, even though the presence or absence of residual disease is already being used to guide adjuvant decisions following NAC (36-38). Another important factor is that neoadjuvant and

adjuvant therapies themselves might mitigate differences between the two groups, reducing adverse events homogeneously. Moreover, newly diagnosed DCIS lesions are a heterogeneous group in morphology, genetics, cellular biology, and clinical behavior. Approximately half of all DCIS lesions progress to an invasive status with an unknown underlying mechanism (39).

This study has several limitations. First, the retrospective design introduces inherent bias and limitations associated with data collection and potential confounding variables. Second, the small sample size may affect the statistical power to detect significant associations between the pathological response and the occurrence of adverse events. In addition, the study was conducted at a single institution, which may limit the generalizability of the findings. Moreover, the extended enrollment period from 2010 to 2021 could introduce a time-based bias, with potential prognostic changes over time due to improvements in therapeutic regimes. Another significant limitation is the lack of data on patient preferences in surgical planning. Understanding patient preferences could provide valuable insights into the decision-making process and improve personalized treatment approaches. Lastly, long-term follow-up data beyond the scope of this study were not available, precluding the evaluation of late recurrences and/or cancer-related mortality.

The current study demonstrated that residual DCIS after NAC (ypTis) does not significantly impact DFS or OS compared to complete pathologic response without residual tumor (ypT0). The findings suggest that residual DCIS should be considered in surgical planning, potentially allowing for BCS in suitable cases, and may inform decisions on adjuvant therapy de-escalation. The study highlights the need for a standardized definition of pCR and further research to refine treatment approaches for better patient outcomes.

Ethics Committee Approval: The Humanitas University Research Committee and Institutional Board approved this retrospective study (approval no.: EC04-06-CT34-NAC, date: 27.05.2024).

Informed Consent: Retrospective study.

Authorship Contributions: Surgical and Medical Practices: C.T., S.S.D., E.B., A.S., V.V., D.G.; Concept: C.T., S.S.D., E.B., A.S., V.V., D.G.; Design: C.T., S.S.D., E.B., A.S., V.V., D.G.; Data Collection and/or Processing: C.T., S.S.D., A.S., V.V., D.G.; Analysis and/or Interpretation: C.T., S.S.D., E.B., D.G.; Literature Search: C.T., S.S.D., D.G.; Writing: C.T., S.S.D., E.B., V.V., D.G.

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

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

References

1. Hortobagyi GN, Ames FC, Buzdar AU, Kau SW, McNeese MD, Paulus D, et al. Management of stage III primary breast cancer with primary chemotherapy, surgery, and radiation therapy. Cancer. 1988; 62: 2507-2516. (PMID: 3056604) [Crossref]
2. Sacchini V, Norton L. Escalating de-escalation in breast cancer treatment. Breast Cancer Res Treat. 2022; 195: 85-90. (PMID: 35902432) [Crossref]
3. Schiavone A, Ventimiglia F, Zarba Meli E, Taffurelli M, Caruso F, Gentilini OD, et al. Third national surgical consensus conference of the Italian Association of Breast Surgeons (ANISC) on management after neoadjuvant chemotherapy: The difficulty in reaching a consensus. Eur J Surg Oncol. 2024; 50: 108351. (PMID: 38701582) [Crossref]
4. Barbieri E, Gentile D, Bottini A, Sagona A, Gatzemeier W, Losurdo A, et al. Neo-Adjuvant Chemotherapy in Luminal, Node Positive Breast Cancer: Characteristics, Treatment and Oncological Outcomes: A Single Center's Experience. Eur J Breast Health. 2021; 17: 356-362. (PMID: 34651115) [Crossref]
5. Cortazar P, Geyer CE. Pathological Complete Response in Neoadjuvant Treatment of Breast Cancer. Ann Surg Oncol. 2015; 22: 1441-1446. (PMID: 25727556) 10.1245/s10434-015-4404-8
6. Kong X, Moran MS, Zhang N, Haffty B, Yang Q. Meta-analysis confirms achieving pathological complete response after neoadjuvant chemotherapy predicts favourable prognosis for breast cancer patients. Eur J Cancer. 2011; 47: 2084-2090. (PMID: 21737257) [Crossref]
7. Tinterri C, Barbieri E, Sagona A, Bottini A, Canavese G, Gentile D. De-Escalation Surgery in cT3-4 Breast Cancer Patients after Neoadjuvant Therapy: Predictors of Breast Conservation and Comparison of Long-Term Oncological Outcomes with Mastectomy. Cancers (Basel). 2024; 16: 1169. (PMID: 38539504) [Crossref]
8. Kerr AJ, Dodwell D, McGale P, Holt F, Duane F, Mannu G, et al. Adjuvant and neoadjuvant breast cancer treatments: A systematic review of their effects on mortality. Cancer Treat Rev. 2022; 105: 102375. (PMID: 35367784) [Crossref]
9. Gentile D, Sagona A, De Carlo C, Fernandes B, Barbieri E, Di Maria Grimaldi S, et al. Pathologic response and residual tumor cellularity after neo-adjuvant chemotherapy predict prognosis in breast cancer patients. Breast. 2023; 69: 323-329. (PMID: 37001289) [Crossref]
10. Takada M, Toi M. Neoadjuvant treatment for HER2-positive breast cancer. Chin Clin Oncol. 2020; 9: 32. (PMID: 32527117) [Crossref]
11. Kuerer HM, Smith BD, Krishnamurthy S, Yang WT, Valero V, Shen Y, et al. Eliminating breast surgery for invasive breast cancer in exceptional responders to neoadjuvant systemic therapy: a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2022; 23: 1517-1524. (PMID: 36306810) [Crossref]
12. Clough KB, Acosta-Marín V, Nos C, Alran S, Rouanet P, Garbay JR, et al. Rates of Neoadjuvant Chemotherapy and Oncoplastic Surgery for Breast Cancer Surgery: A French National Survey. Ann Surg Oncol. 2015; 22: 3504-3511. (PMID: 25665949) [Crossref]
13. Vugts G, Maaskant-Braat AJG, Nieuwenhuijzen GAP, Roumen RMH, Luiten EJT, Voogd AC. Patterns of care in the administration of neo-adjuvant chemotherapy for breast cancer. A population-based study. Breast J. 2016; 22: 316-321. (PMID: 26945566) [Crossref]
14. Golshan M, Cirrincione CT, Sikov WM, Berry DA, Jasinski S, Weisberg TF, et al. Impact of neoadjuvant chemotherapy in stage II-III triple negative breast cancer on eligibility for breast-conserving surgery and breast conservation rates: Surgical results from CALGB 40603 (Alliance). Ann Surg. 2015; 262: 434-439; discussion 438-439. (PMID: 26222764) [Crossref]
15. Galimberti V, Vicini E, Corso G, Morigi C, Fontana S, Sacchini V, et al. Nipple-sparing and skin-sparing mastectomy: Review of aims, oncological safety and contraindications. Breast. 2017; 34: S82-S84. (PMID: 28673535) [Crossref]
16. Zarba Meli E, De Santis A, Cortese G, Manna E, Mastropietro T, La Pinta M, et al. Nipple-Sparing Mastectomy After Neoadjuvant Chemotherapy: Definitive Results with a Long-Term Follow-Up Evaluation. Ann Surg Oncol. 2023; 30: 2163-2172. (PMID: 36598627) [Crossref]
17. Scardina L, Di Leone A, Biondi E, Carnassale B, Sanchez AM, D'Archi S, et al. Prepectoral vs. Submuscular Immediate Breast Reconstruction in Patients Undergoing Mastectomy after Neoadjuvant Chemotherapy: Our Early Experience. J Pers Med. 2022; 12: 1533. (PMID: 36143318) [Crossref]

18. Pinder SE, Provenzano E, Earl H, Ellis IO. Laboratory handling and histology reporting of breast specimens from patients who have received neoadjuvant chemotherapy. Histopathology. 2007; 50: 409-417. (PMID: 17448015) [Crossref]
19. Provenzano E. Neoadjuvant Chemotherapy for Breast Cancer: Moving Beyond Pathological Complete Response in the Molecular Age. Acta Med Acad. 2021; 50: 88-109. (PMID: 34075766) [Crossref]
20. Schwartz LH, Litière S, De Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1 - Update and clarification: From the RECIST committee. Eur J Cancer. 2016; 62: 132-137. (PMID: 27189322) [Crossref]
21. Giuliano AE, Edge SB, Hortobagyi GN. Eighth Edition of the AJCC Cancer Staging Manual: Breast Cancer. Ann Surg Oncol. 2018; 25: 1783-1785. (PMID: 29671136) [Crossref]
22. Sataloff DM, Mason BA, Prestipino AJ, Seinige UL, Lieber CP, Baloch Z. Pathologic response to induction chemotherapy in locally advanced carcinoma of the breast: A determinant of outcome. J Am Coll Surg. 1995; 180: 297-304. (PMID: 7874340) [Crossref]
23. Symmans WF, Peintinger F, Hatzis C, Rajan R, Kuerer H, Valero V, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol. 2007; 25: 4414-4422. (PMID: 17785706) [Crossref]
24. Litton JK, Regan MM, Pusztai L, Rugo HS, Tolaney SM, Garrett-Mayer E, et al. Standardized Definitions for Efficacy End Points in Neoadjuvant Breast Cancer Clinical Trials: NeoSTEEP. J Clin Oncol. 2023; 41: 4433-4442. (PMID: 37433103) [Crossref]
25. Marinovich ML, Macaskill P, Irwig L, Sardanelli F, von Minckwitz G, Mamounas E, et al. Meta-analysis of agreement between MRI and pathologic breast tumour size after neoadjuvant chemotherapy. Br J Cancer 2013; 109: 1528-1536. (PMID: 23963140) [Crossref]
26. Goldberg H, Zandbank J, Kent V, Leonov-Polak M, Livoff A, Chernihovsky A, et al. Chemotherapy may eradicate ductal carcinoma in situ (DCIS) but not the associated microcalcifications. Eur J Surg Oncol. 2017; 43: 1415-1420. (PMID: 28526187) [Crossref]
27. Conforti F, Pala L, Sala I, Oriecuia C, De Pas T, Specchia C, et al. Evaluation of pathological complete response as surrogate endpoint in neoadjuvant randomised clinical trials of early stage breast cancer: Systematic review and meta-analysis. BMJ. 2021; 375: e066381. (PMID: 34933868) [Crossref]
28. Burstein HJ. Systemic Therapy for Estrogen Receptor–Positive, HER2-Negative Breast Cancer. Longo DL, editor. N Engl J Med. 2020; 383: 2557-2570. (PMID: 33369357) [Crossref]
29. Castaneda SA, Strasser J. Updates in the Treatment of Breast Cancer with Radiotherapy. Surg Oncol Clin N Am. 2017; 26: 371-382. (PMID: 28576177) [Crossref]
30. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet. 2014; 384: 164-172. (PMID: 24529560) [Crossref]
31. von Minckwitz G, Rezai M, Loibl S, Fasching PA, Huober J, Tesch H, et al. Capecitabine in Addition to Anthracycline- and Taxane-Based Neoadjuvant Treatment in Patients With Primary Breast Cancer: Phase III GeparQuattro Study. J Clin Oncol. 2010; 28: 2015-2023. (PMID: 20308671) [Crossref]
32. von Minckwitz G, Untch M, J Blohmer U, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012; 30: 1796-1804. (PMID: 22508812) [Crossref]
33. Symmans WF, Wei C, Gould R, Yu X, Zhang Y, Liu M, et al. Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype. J Clin Oncol. 2017; 35: 1049-1060. (PMID: 28135148) [Crossref]
34. Broglio KR, Quintana M, Foster M, Olinger M, McGlothlin A, Berry SM, et al. Association of pathologic complete response to neoadjuvant therapy in HER2- positive breast cancer with long-term outcomes ameta-analysis. JAMA Oncol. 2016; 2: 751-760. (PMID: 26914222) [Crossref]
35. Yoshioka T, Hosoda M, Yamamoto M, Taguchi K, Hatanaka KC, Takakuwa E, et al. Prognostic significance of pathologic complete response and Ki67 expression after neoadjuvant chemotherapy in breast cancer. Breast Cancer. 2015; 22: 185-191. (PMID: 23645542) [Crossref]
36. Yau C, Osdoit M, van der Noordaa M, Shad S, Wei J, de Croze D, et al. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. Lancet Oncol. 2022; 23: 149-160. (PMID: 34902335) [Crossref]
37. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med. 2017; 376: 2147-2159. (PMID: 28564564) [Crossref]
38. von Minckwitz G, Huang C-S, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019; 380: 617-628. (PMID: 30516102) [Crossref]
39. Hophan SL, Odnokoz O, Liu H, Luo Y, Khan S, Gradishar W, et al. Ductal Carcinoma In Situ of Breast: From Molecular Etiology to Therapeutic Management. Endocrinology. 2022; 163. (PMID: 35245349) [Crossref]

Original Article

Eur J Breast Health 2024; 20(4): 284-291
DOI: 10.4274/ejbh.galenos.2024.2024-4-3

Overexpression of *CDC25A*, *AURKB*, and *TOP2A* Genes Could Be an Important Clue for Luminal A Breast Cancer

Murat Kaya[1], Asmaa Abuaisha[2], İlknur Süer[3], Melike Sultan Alptekin[4], Fahrünnisa Abanoz[2], Selman Emiroğlu[5,6], Şükrü Palanduz[1], Kıvanç Cefle[1], Şükrü Öztürk[1]

[1]Division of Medical Genetics, Department of Internal Medicine, İstanbul Faculty of Medicine, İstanbul University, İstanbul, Turkey
[2]Department of Genetics, Institute of Graduate Studies in Health Sciences, İstanbul University, İstanbul, Turkey
[3]Department of Medical Genetics Department, İstanbul Faculty of Medicine, İstanbul University, İstanbul, Turkey
[4]Department of Molecular Biology and Genetics, İstanbul Health and Technology University, İstanbul, Turkey
[5]Division of Breast Surgery, Department of General Surgery, İstanbul Faculty of Medicine, İstanbul University, İstanbul, Turkey
[6]Department of Molecular and Medical Genetics, Graduate School of Education, Biruni University, İstanbul, Turkey

ABSTRACT

Objective: Breast cancer (BC) is highly heterogeneous and one of the most common cancers. Luminal A (LUM A) is a subtype of BC with a better prognosis than other BC subtypes. The molecular mechanisms underlying the initiation and progression of the LUM A subtype are still unclear. Big data generated from microarray and sequencing systems can be re-analyzed, especially with the help of various *in silico* tools developed in recent years, and made applicable for *in vitro* and *in vivo* research. This work aimed to identify genes that may play a role in the progression of LUM A subtype of BC using both computational and laboratory-based methods.

Materials and Methods: Overlapping genes associated with BC were identified from the The Cancer Genome Atlas database, GSE233242, GSE100925 geodata sets, and the geneshot tool. The network functional analysis between overlapping genes was determined with STRING 12.0. Expression levels of overlapping genes in BC were investigated with the TNMplot (https://tnmplot.com/analysis/) *in silico* tool. The effect of overlapping genes on the overall survival of LUM A cancer patients was defined using the Kaplan-Meier plotter tool. Expressions of genes identified using bioinformatics data were investigated via quantitative real-time -polymerase chain reaction (qRT-PCR) in LUM A tumor and adjacent tissue samples. The data were evaluated using the t-test. Both the sensitivity and specificity of selected genes have been determined using the receiver operating characteristic curve.

Results: *In silico* investigation showed that eleven genes were possibly associated with BC. Among them *CDC25A*, *AURKB*, and *TOP2A* were considerably increased in LUM A samples according to qRT-PCR results. An overall survival analysis also showed that overexpression of these three genes could reduce the overall survival of LUM A patients.

Conclusion: The genes *CDC25A*, *AURKB*, and *TOP2A* may play crucial functions in LUM A pathogenesis. Therapeutic strategies that diminish the expression of these connected genes may enhance the prognosis of LUM A patients.

Keywords: Bioinformatics; CDC25A; AURKB; TOP2A; luminal A

Cite this article as: Kaya M, Abuaisha A, Süer I, Alptekin MS, Abanoz F, Emiroğlu S, Palanduz Ş, Cefle K, Öztürk Ş. Overexpression of *CDC25A*, *AURKB*, and *TOP2A* Genes Could Be an Important Clue for Luminal A Breast Cancer. Eur J Breast Health. 2024; 20(4): 284-291

Key Points

- Overexpression of CDC25A.
- AURKB.
- TOP2A can be potential biomarkers for luminal A.

Introduction

Breast cancer (BC) is the most prevalent cancer in women globally, accounting for the second-greatest percentage of cancer-related fatalities among women. BC is a disease that varies greatly regarding morphological and biological characteristics, clinical behavior, and therapeutic responses (1, 2). Currently, BC has been classified molecularly as luminal A (LUM A), luminal B (LUM B), human epidermal growth factor receptor 2 positive (HER2+), triple-negative BC (TNBC), and normal breast-like (3). According to investigations, further categorizing these subgroups is possible and important. Approximately 70% of BC patients suffer from the LUM A subtype, which has a positive estrogen receptor (ER+) but lacks an amplification of the HER2 (4). LUM A tumors have a decreased

Corresponding Author:
Murat Kaya; kmurat@istanbul.edu.tr

Received: 18.04.2024
Accepted: 07.08.2024
Available Online Date: 26.09.2024

probability of recurrence compared to other subtypes of BC. However, there is still a need to understand the mechanisms behind the onset and progression of the LUM A subtype, which has a variable prognosis (5). Since the tumor is hormone receptor-positive, endocrine therapy is effectively preferred in the treatment of LUM A BC. However, the efficacy of endocrine therapy for LUM A may differ based on several genetic factors (6). For example, it was proposed that *GATA3* mutations may result in altered gene expression in ER-positive BCs, which might influence prognosis (7). Alfarsi et al. (8) showed that high *KIF18A* expression is a prognostic factor and can predict adverse outcomes of endocrine treatment in individuals with ER-positive BC. Therefore, identifying differently expressed genes may be valuable for more precise categorization, clarification of molecular pathways, and improving disease treatment success rates in the future. In the current study, a bioinformatic approach was used to identify overlapping genes within two BC-related datasets, The Cancer Genome Atlas (TCGA) and BC-relevant genes. Several *in silico* tools were used to conduct an enrichment analysis of overlapping genes. The expression of three overlapping genes was further investigated using the quantitative real-time -polymerase chain reaction (qRT-PCR) method in tumor and adjacent normal tissue samples from 30 LUM A cancer patients. Then the results were evaluated using receiver operating characteristic (ROC) analysis.

Materials and Methods

Using Bioinformatics Approaches to Uncover BC-Associated Genes

Analysis of Gene Expression Alterations in TCGA BC Samples

TCGA (https://cancergenome.nih.gov/) is a very important database in which approximately 20,000 primary tumors and adjacent samples of dozens of different cancer types are molecularly analyzed. The TCGA-BC data was analyzed using the GEPIA2 online tool (http://gepia2.cancer-pku.cn/) to determine significant genes. The "Differential Expression Analysis" option was initially selected in the GEPIA2 online tool. The research was subsequently conducted by selecting "Breast cancer" in the dataset section and "ANOVA" in the method selection section on the opened page. Overexpressed genes in TCGA-BC data were identified with log fold change (logFC) >+1 and p<0.001 criterion.

Detection of Gene Expression Changes in BC- Gene Expression Omnibus Datasets

Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/gds) is a publicly available source of functional genomics data. Microarrays or sequence-based studies' results are accepted in the GEO database. Using the GEO database, GEO datasets related to many diseases can be downloaded and the expression profiles can be reanalyzed. The GSE233242 (29 LUM A tumor tissues and adjacent normal tissue samples) and GSE100925 (36 BC tumor tissue samples and adjacent normal tissue samples) GEO datasets were obtained from the GEO database and analyzed using GEO2R. GEO2R is a user-friendly online tool that allows users to compare multiple data sets from a GEO series to identify differently expressed genes, miRNAs, circRNAs and other molecules. Among GEO2R analysis results genes with logFC >+1 and p<0.001 were defined.

Determination of the Most Closely BC-associated Genes

Geneshot is a free, publicly available tool that allows researchers to obtain ranked lists of genes related to search terms (9). The Geneshot tool was used to screen for BC-associated genes. The search query "Breast cancer" was inputted in the "Search for these terms" field, and the number "500" was entered in the "Top Associated Genes to Make Predictions" search field in Geneshot. Subsequently, the option "AutoRIF (automatically search from PubMed)" was chosen.

Determination of Overlapping Genes

Overlapping BC-related genes were identified in the TCGA database, GSE233242, GSE100925 geo datasets, and the Geneshot tool. Then, a Venn diagram was generated using the Functional Enrichment tool (http://www.funrich.org/).

Enrichment Analyses of Overlapping Genes

STRING 12.0 (https://string-db.org/) is a software tool and knowledgebase for identifying and predicting protein-protein interactions. The network functional analysis between overlapping genes was determined with STRING 12.0 tool. TNMplot (https://tnmplot.com/analysis/) is a free and publicly available tool that allows differential gene expression analysis in tumor tissues, normal tissues, and metastatic tissues using TCGA, GEO, and GTEx data. Expression levels of overlapping genes in BC were investigated with the TNMplot *in silico* tool. Kaplan-Meier plotter (KM plotter) (https://kmplot.com/analysis/) is a web-based tool designed to evaluate the expression and survival rates of genes/miRNAs in various forms of cancer, using publicly available transcriptome data such as TCGA. The effect of overlapping genes on the overall survival (OS) of LUM A patients was defined using the KM plotter tool. TCGA-BC data was utilized to evaluate Spearman correlation analysis of three overlapping genes in bioinformatics data (via GEPIA2).

Verification of Bioinformatics-Derived Data

Patients and Specimens

From November 2020 to November 2022, 30 pairs of human BC specimens (tumor tissues and adjacent normal tissues) were obtained from patients who underwent breast surgery at the İstanbul Faculty of Medicine Hospital, Department of General Surgery, İstanbul University (İstanbul, Turkey), The study was approved by the Ethics and Scientific Committees of İstanbul Faculty of Medicine, İstanbul University (number: 29624016-050.99-903, date: 01.07.2020). Written informed consent from all the patients was obtained.

Investigation of the Chosen Genes' Relative Expressions Using QRT-PCR

Total RNAs from 30 pairs of LUM A tissue samples were extracted with TRIzol reagent (Invitrogen, San Diego, CA, USA) following the manufacturer's instructions. A NanoDrop spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) was used to evaluate the quality and amount of RNA samples. To investigate the expression of chosen genes the same amount of RNA from the samples was reverse transcribed into cDNA using the cDNA Reverse Transcription Kit (Thermo). qRT-PCR experiments were conducted using 5x HOT FIRE qPCR Mix Plus (Solis BioDyne, Tartu, Estonia). GAPDH expression was used to normalize gene expression. Each reaction was conducted at least twice. Relative gene expressions were calculated using the $2^{-\Delta\Delta Ct}$ method. Both the sensitivity and specificity of genes were determined using the receiver operating characteristic (ROC) curve.

Statistical Analysis

Bioinformatic evaluations were performed using publicly available platforms. The current study employed the $2^{-\Delta\Delta Ct}$ method to evaluate gene expression levels between tumor specimens and adjacent normal tissue groups. Data are presented as mean ± standard deviation. Data were analyzed using GraphPad Prism version 10.0 (www.graphpad.com). A statistically significant difference was defined as $p<0.05$. The ROC curves, the area under the ROC curve, the cut-off point, sensitivity, and specificity for all genes were calculated.

Results

Bioinformatics Analyzes Showed an Overlap of 11 Genes in Datasets

Eleven genes in the TCGA-BC database GSE233242, GSE100925 geo datasets, and Geneshot tool overlapped with logFC>+1 and $p<0.001$ criterion (Table 1).

Used Bioinformatics Data in the Current Study Show 11 Genes Were Closely Associated With BC

The TCGA-BC database has 250 genes, whereas the GSE233242 dataset contains 1858 genes and the GSE100925 dataset contains 257 genes that match the logFC>+1, $p<0.001$ criterion. These genes were compared to the 500 most BC-associated genes in the Geneshot tool, and 11 of them overlapped (Figure 1A). As a result of the network analysis performed through STRING 12.0, it was determined that the interactions between overlapping genes were more than expected. ($p<1.0e-16$) (Figure 1B). The findings of TCGA-BC RNA-seq data analysis using TNMplot revealed that the expression of all 11 genes was higher in tumor and metastatic tissue samples than in normal tissues (Figure 1C). Moreover, when the keywords "Breast cancer, gene names" were searched in PubMed, it was found that all of these genes were associated with BC. Remarkably, a profoundly meaningful relationship was seen among the 11 chosen genes. These findings imply that developing specific therapy approaches to inhibit gene expression might be beneficial.

Overlapping Genes May Be Biomarkers for LUM A Overall Survival

OS analysis using the KM plotter tool demonstrated that overexpression of overlapping genes other than *PLK1* significantly affected LUM A OS (Figure 2). Three of the overlapping genes were strongly correlated with each other. According to the Spearman correlation analysis carried out on TCGA-BC data using GEPIA2, the *CDC25A*, *AURKB*, and *TOP2A* genes are most likely to be co-expressed (Figure 3). According to qRT-PCR results, all three selected genes (*CDC25A*, *AURKB*, *TOP2A)* were found to have increased expression in LUM A tumor samples compared to adjacent normal tissue samples (Figure 4). We employed a ROC curve study to determine whether selected genes may be utilized as prognostic biomarkers. Our findings indicated that *CDC25A*, *AURKB*, and *TOP2A* are promising LUM A indicators (Figure 5).

Discussion and Conclusion

Studies have revealed that BC is a very heterogeneous cancer at the molecular level (2, 10). There is a need to elucidate the molecular mechanisms more clearly to develop treatment strategies. Concurrently, with the advances in microarray and sequencing technologies in recent years, a substantial volume of raw data regarding several types of malignancies, including BC, has been accumulated. Validating all this huge data *in vitro* or *in vivo* is a highly difficult and costly undertaking. Consequently, several *in silico* tools have been developed to aid in the filtration and processing of this data. Thus, using *in silico* tools, many genes/miRNAs and other molecules that may play a role in BC have been suggested (11-13). In the current investigation, we employed some *in silico* tools to identify genes that may be linked to LUM A. These genes were subsequently verified in LUM A patient samples.

Studies demonstrated that all 11 genes we identified with bioinformatics methods in our study are closely related to BC. For example, *BIRC5* has been reported to mediate poor response to radiotherapy in HER2-positive BCs (14). Elevated *CCNB1* expression has been related to a poor prognosis and tumor immune infiltration in BC (15). It has been shown that successful treatment results can be achieved in BC subtypes

Table 1. Overlapping genes' logFC and *p*-values in GSE233242, GSE100925 datasets, and TCGA-BC

	GSE233242		GSE100925		TCGA-BC	
Genes	***p*-value**	**logFC**	***p*-value**	**logFC**	***p*-value**	**logFC**
PLK1	2.37e-08	1.64	2.07E-22	3.19	7.23e-158	2.64
BIRC5	1.93e-06	2.01	1.21E-15	3.24	1.26e-186	3.40
TOP2A	1.84e-07	2.41	7.47E-21	3.21	5.24e-210	3.90
CCNB1	3.48e-11	1.71	8.92E-22	2.45	9.81e-209	2.98
AURKA	1.15e-10	2.02	1.23E-21	2.84	7.11e-174	2.77
CDK1	2.06e-12	2.24	1.70E-19	2.64	2.82e-184	2.84
RAD51	4.02e-07	1.59	3.40E-14	2.13	6.27e-152	2.23
FOXM1	4.76e-06	1.51	2.24E-18	2.89	1.34e-160	2.90
CCNA2	7.77e-10	1.62	3.00E-17	2.48	2.48e-130	2.09
CDC25A	4.96e-06	1.36	2.38E-10	2.02	4.85e-770	1.21
AURKB	6.56e-05	1.59	5.26E-19	2.96	5.92e-145	2.67

logFC: Log fold change; TCGA: The Cancer Genome Atlas; BC: Breast cancer

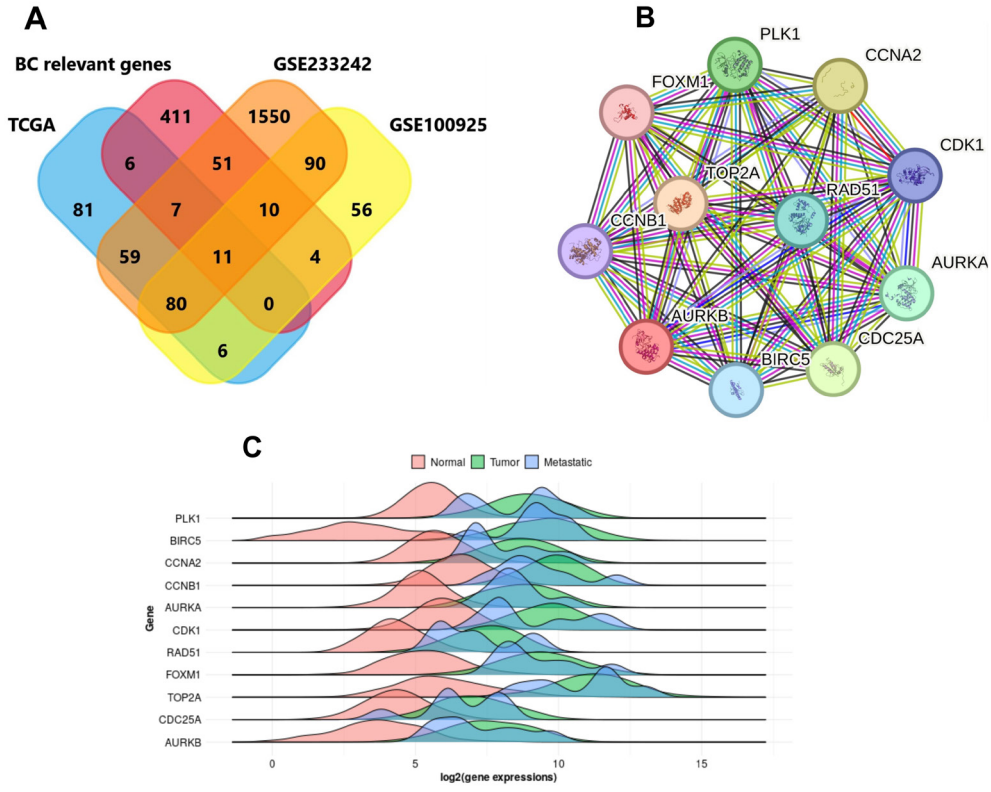

Figure 1. Enrichment analysis of 11 overlapping genes. **A.** Venn diagram showing overlapping genes in TCGA-BC database, GSE233242, GSE100925 datasets, and Geneshot tool. **B.** The string interaction network of the overlapping genes in datasets. (number of nodes:11, number of edges: 55, average node degree: 10. PPI enrichment *p*-value≤1.0e−16). **C.** Density expressions' plot of overlapping genes. TNMplot RNASeq data

TCGA: The Cancer Genome Atlas; BC: Breast cancer; PPI: Protein-protein interactions

by targeting the transcription factor FOXM1, which has an oncogenic effect in BC (16). However, the status of these genes' expression and roles in LUM A are unclear. Moreover, in our study, the co-expression scores of these genes were found to be higher than expected (Figure 1B), and the significant potential of these genes to play a role in LUM A-OS indicates that they may be of critical importance for LUM A (Figure 2). Identifying genes that have similar functions within the cell and exhibit stronger interactions with each other is crucial for understanding molecular pathways. Thus, our research findings are valuable and the suggested genes can be regarded as indicators for elucidating the molecular mechanisms involved in developing LUM A. Therefore, more detailed studies are needed to elucidate the roles of these genes in the LUM A subtype.

The expression levels of *CDC25A*, *AURKB*, and *TOP2A*, among the overlapping 11 genes detected using bioinformatics methods, were investigated in 30 LUM A specimens by qRT-PCR. It was observed that all three genes were overexpressed in LUM A tumor samples compared to the control group. Moreover, the expressions of these genes were found to be reliable in the ROC curves. These findings suggest that these three genes may play important roles in the LUM A subtype.

CDC25A is a cell cycle accelerating phosphatase and increased expression of this gene has been associated with many cancers (17). Although studies have clearly shown the relationship between CDC25A and BC the function of CDC25A in LUM A remains unclear (18). *CDC25A* is involved in the BC process with many genes and miRNAs. For example, in the study of Feng et al. (19), it was shown that *CDC25A* participated in the BC metastasis process by controlling matrix metalloprotease 1 through Foxo1. Ectopic miR-100-5p expression has been demonstrated to reduce BC cell proliferation, migration, and invasion while increasing apoptosis via inhibiting the expression of *CDC25A* (20). MicroRNA-99a-5p has been reported to suppress BC progression and cell cycle pathways by downregulating *CDC25A* (21).

The *AURKB* gene is also closely associated with BC. For instance, it has been shown that polymorphisms in the *AURKB* gene can predict the OS or disease-free survival of TNBC patients treated with taxane-based adjuvant chemotherapy (22). O6-benzyl guanine, an ethylguanine-DNA methyl transferase (MGMT) inhibitor, has been shown to reduce the expression of many genes, including *TOP2A* and *AURKB*, sensitizing ER-positive BC to temozolomide (23). Another study suggested that *NEK2*, *BIRC5*, and *TOP2A* genes may be potential targets in obese patients with LUM A BC (24).

TOP2A is an isoform of TOP2, a nuclear protein that plays an important role in DNA replication and cell division. *TOP2A* is highly expressed in proliferating and growing cells, and overexpression of this gene has been detected in various human malignancies, such as hepatocellular carcinoma, primary BC, and colon cancer (25).

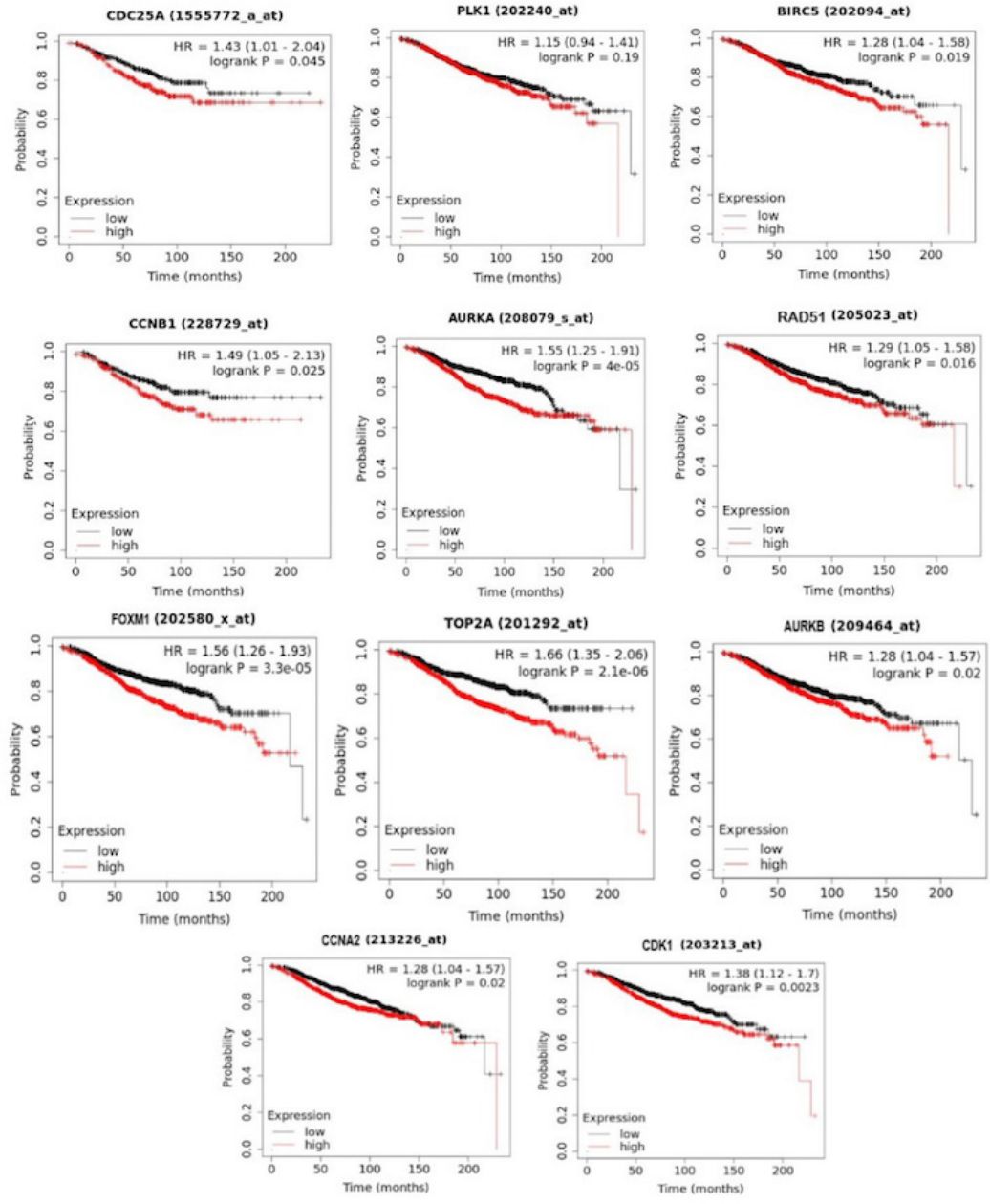

Figure 2. The overlapping genes' exp. on LUM A patients' OS via KM plotter tool. Except for PLK1, increasing the expression of the other ten genes has an unfavorable impact on LUM A OS

LUM A: Luminal A; OS: Overall survival; KM: Kaplan-Meier

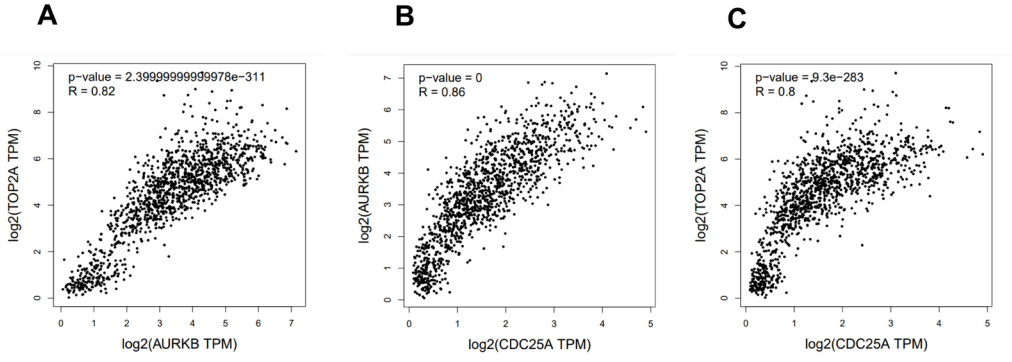

Figure 3. Correlation analysis of **A.** *AURKB-TOP2A*, **B.** *CDC25A-AURKB*, **C.** *CDC25A-TOP2A* genes

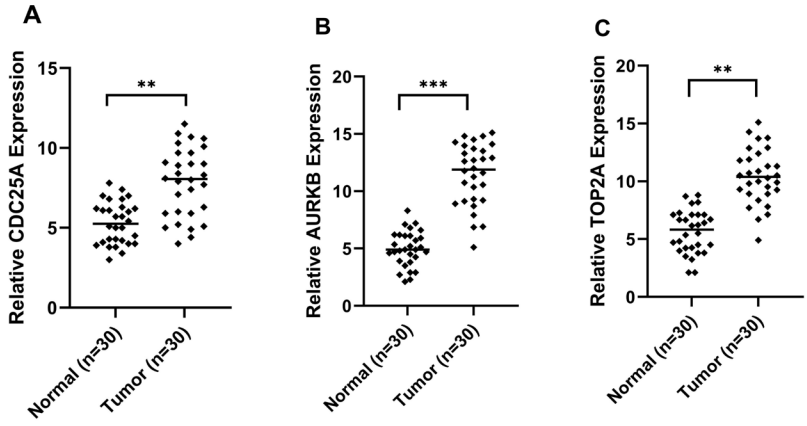

Figure 4. The relative mRNA expression levels of **A.** CDC25A, **B.** AURKB, and **C.** TOP2A in LUM A cancer tissues and adjacent normal tissues
**: $p<0.01$ and ***: $p<0.001$ (GAPDH expression was employed as an internal control for evaluating mRNA expression)
LUM A: Luminal A

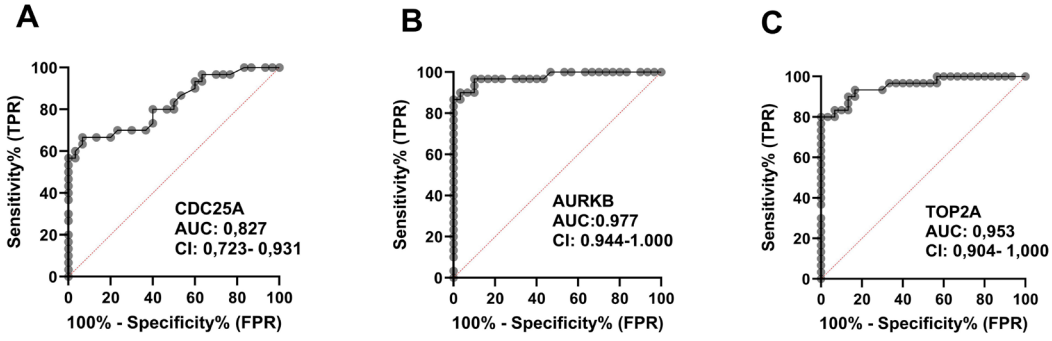

Figure 5. ROC curve analysis of **A.** CDC25A, **B.** AURKB, **C.** *TOP2A* genes in LUM A. $p<0,05$
TPR: True positive rate; FPR: False positive rate; AUC: Area under the curve; CI: Confidence interval; ROC: Receiver operating characteristic; LUM A: Luminal A

Several TOP2A inhibitors have been used to treat different malignancies (25, 26). Studies have shown that the expression alteration of *TOP2A*, which is targeted by multiple microRNAs and long non-coding RNAs, has a role in cancer processes. For example, a study targeting the long non-coding RNA MALAT1 demonstrated that BC cells were suppressed via the microRNA-561-3p/*TOP2A* axis (27). Although it is known that *TOP2A* generally shows increased expression levels in BC, there is not enough data regarding its expression level in LUM A patients (24, 28).

The expression of genes can be controlled in several ways (29-31). Non-codingRNAs, such as microRNAs and circular RNAs, are crucial molecules that regulate gene expression (32-34). Studies demonstrated that alterations in the expression of these noncoding RNAs can be important in several cancer processes via many targeted genes (35).

Although non-coding RNAs have not yet been employed in therapy, it is anticipated that they may have enormous potential in the future. In recent years, several inhibitors have been discovered to decrease the expression of overexpressed genes in the cell. We believe that therapy methods can be developed in the future by inhibiting the expression of genes such as *CDC25A*, *AURKB*, and *TOP2A* in LUM A cancer utilizing different inhibitors and/or noncoding RNAs. Further studies can be performed using *in vitro* and *in vivo* methods to silence the expression of these genes and uncover their functional implications on cancer processes. Therefore, our findings will provide hints for future in vitro and *in vivo* investigations.

Ethics Committee Approval: The study was approved by the Ethics and Scientific Committees of İstanbul Faculty of Medicine, İstanbul University (number: 29624016-050.99-903, date: 01.07.2020).

Informed Consent: Written informed consent from all the patients was obtained.

Authorship Contributions

Concept: M.K.; Design: M.K., A.A., F.A., Ş.Ö.; Data Collection and/or Processing: M.K., A.A., İ.S., F.A., Ş.P.; Analysis and/or Interpretation: M.K., Ş.P., K.C., Ş.Ö.; Literature Search: M.K., İ.S., M.S.A., F.A., S.E.; Writing: M.K., A.A., M.S.A., S.E., K.C.

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

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

References

1. van Maaren MC, de Munck L, Strobbe LJA, Sonke GS, Westenend PJ, Smidt ML, et al. Ten-year recurrence rates for breast cancer subtypes in the Netherlands: A large population-based study. Int J Cancer. 2019; 144: 263-272. (PMID: 30368776) [Crossref]
2. Kaya M, Abuaisha A, Suer I, Emiroglu S, Abanoz F, Palanduz S, et al. Turmeric Inhibits MDA-MB-231 Cancer Cell Proliferation, Altering miR-638-5p and Its Potential Targets. Eur J Breast Health. 2024; 20: 102-109. (PMID: 38571691) [Crossref]
3. Gao JJ, Swain SM. Luminal A Breast Cancer and Molecular Assays: A Review. Oncologist. 2018; 23: 556-565. (PMID: 29472313) [Crossref]
4. Anderson DH. Luminal A breast cancer resistance mechanisms and emerging treatments. Biological mechanisms and the advancing approaches to overcoming cancer drug resistance: Elsevier. 2021. p. 1-22. [Crossref]
5. Wang S, Lee D. Identifying prognostic subgroups of luminal-A breast cancer using deep autoencoders and gene expressions. PLoS Comput Biol. 2023; 19: e1011197. (PMID: 37253056) [Crossref]
6. Jia R, Li Z, Liang W, Ji Y, Weng Y, Liang Y, et al. Identification of key genes unique to the luminal a and basal-like breast cancer subtypes via bioinformatic analysis. World J Surg Oncol. 2020; 18: 268. (PMID: 33066779) [Crossref]
7. Karn R, Emerson IA. Breast cancer mutation in GATA3 zinc finger 1 induces conformational changes leading to the closer binding of ZnFn2 with a wrapping architecture. J Biomol Struct Dyn. 2020; 38: 1810-1821. (PMID: 31107186) [Crossref]
8. Alfarsi LH, Elansari R, Toss MS, Diez-Rodriguez M, Nolan CC, Ellis IO, et al. Kinesin family member-18A (KIF18A) is a predictive biomarker of poor benefit from endocrine therapy in early ER+ breast cancer. Breast Cancer Res Treat. 2019; 173: 93-102. (PMID: 30306428) [Crossref]
9. Lachmann A, Schilder BM, Wojciechowicz ML, Torre D, Kuleshov MV, Keenan AB, et al. Geneshot: search engine for ranking genes from arbitrary text queries. Nucleic Acids Res. 2019; 47: W571-w7. (PMID: 31114885) [Crossref]
10. Lüönd F, Tiede S, Christofori G. Breast cancer as an example of tumour heterogeneity and tumour cell plasticity during malignant progression. Br J Cancer. 2021; 125: 164-175. (PMID: 33824479) [Crossref]
11. Jayanthi V, Das AB, Saxena U. Grade-specific diagnostic and prognostic biomarkers in breast cancer. Genomics. 2020; 112: 388-396. (PMID: 30851359) [Crossref]
12. Erdogan C, Suer I, Kaya M, Ozturk S, Aydin N, Kurt Z. Bioinformatics analysis of the potentially functional circRNA-miRNA-mRNA network in breast cancer. PLoS One. 2024; 19: e0301995. (PMID: 38635539) [Crossref]
13. Kaya M. A Bioinformatics Approach to Male Infertility, MicroRNAs, and Targeted Genes. Ahi Evran Medical Journal. 2023; 7: 296-303. [Crossref]
14. Kim JS, Kim HA, Seong MK, Seol H, Oh JS, Kim EK, et al. STAT3-survivin signaling mediates a poor response to radiotherapy in HER2-positive breast cancers. Oncotarget. 2016; 7: 7055-7065. (PMID: 26755645) [Crossref]
15. Fu H, Li K, Wang S, Li Y. High expression of CCNB1 driven by ncRNAs is associated with a poor prognosis and tumor immune infiltration in breast cancer. Aging (Albany NY). 2022; 14: 6780-6795. (PMID: 36040381) [Crossref]
16. Katzenellenbogen BS, Guillen VS, Katzenellenbogen JA. Targeting the oncogenic transcription factor FOXM1 to improve outcomes in all subtypes of breast cancer. Breast Cancer Res. 2023; 25: 76. (PMID: 37370117) [Crossref]
17. Shen T, Huang S. The role of Cdc25A in the regulation of cell proliferation and apoptosis. Anticancer Agents Med Chem. 2012; 12: 631-639. (PMID: 22263797) [Crossref]
18. Cangi MG, Cukor B, Soung P, Signoretti S, Moreira G, Ranashinge M, et al. Role of the Cdc25A phosphatase in human breast cancer. J Clin Invest. 2000; 106: 753-761. (PMID: 10995786) [Crossref]
19. Feng X, Wu Z, Wu Y, Hankey W, Prior TW, Li L, et al. Cdc25A regulates matrix metalloprotease 1 through Foxo1 and mediates metastasis of breast cancer cells. Mol Cell Biol. 2011; 31: 3457-3471. (PMID: 21670150) [Crossref]
20. Li X, Ren Y, Liu D, Yu X, Chen K. Role of miR-100-5p and CDC25A in breast carcinoma cells. PeerJ. 2022; 9: e12263. (PMID: 35036112) [Crossref]
21. Qin H, Liu W. MicroRNA-99a-5p suppresses breast cancer progression and cell-cycle pathway through downregulating CDC25A. J Cell Physiol. 2019; 234: 3526-3537. (PMID: 30443946) [Crossref]
22. Liao Y, Liao Y, Li J, Li J, Fan Y, Xu B. Polymorphisms in AURKA and AURKB are associated with the survival of triple-negative breast cancer patients treated with taxane-based adjuvant chemotherapy. Cancer Manag Res. 2018; 10: 3801-3808. (PMID: 30288111) [Crossref]
23. Bobustuc GC, Kassam AB, Rovin RA, Jeudy S, Smith JS, Isley B, et al. MGMT inhibition in ER positive breast cancer leads to CDC2, TOP2A, AURKB, CDC20, KIF20A, Cyclin A2, Cyclin B2, Cyclin D1, ERα and Survivin inhibition and enhances response to temozolomide. Oncotarget. 2018; 9: 29727-29742. (PMID: 30038716) [Crossref]
24. Nuncia-Cantarero M, Martinez-Canales S, Andrés-Pretel F, Santpere G, Ocaña A, Galan-Moya EM. Functional transcriptomic annotation and protein-protein interaction network analysis identify NEK2, BIRC5, and TOP2A as potential targets in obese patients with luminal A breast cancer. Breast Cancer Res Treat. 2018; 168: 613-623. (PMID: 29330624) [Crossref]
25. Wang T, Lu J, Wang R, Cao W, Xu J. TOP2A promotes proliferation and metastasis of hepatocellular carcinoma regulated by miR-144-3p. J Cancer. 2022; 13: 589-601. (PMID: 35069905) [Crossref]
26. Delgado JL, Hsieh CM, Chan NL, Hiasa H. Topoisomerases as anticancer targets. Biochem J. 2018; 475: 373-398. (PMID: 29363591) [Crossref]
27. Hajibabaei S, Nafissi N, Azimi Y, Mahdian R, Rahimi-Jamnani F, Valizadeh V, et al. Targeting long non-coding RNA MALAT1 reverses cancerous phenotypes of breast cancer cells through microRNA-561-3p/TOP2A axis. Sci Rep. 2023; 13: 8652. (PMID: 37244966) [Crossref]
28. Lee SB, Pan J, Xiong D, Palen K, Johnson B, Lubet RA, et al. Striking efficacy of a vaccine targeting TOP2A for triple-negative breast cancer immunoprevention. NPJ Precis Oncol. 2023; 7: 108. (PMID: 37880313) [Crossref]
29. Sato W, Rasmussen M, Gaut N, Devarajan M, Stokes K, Deich C, et al. A gene expression control technology for cell-free systems and synthetic cells via targeted gene silencing and transfection. Biotechnol Bioeng. 2023; 120: 1986-1997. (PMID: 37159417) [Crossref]
30. Fracassi C, Postiglione L, Fiore G, di Bernardo D. Automatic Control of Gene Expression in Mammalian Cells. ACS Synth Biol. 2016; 5: 296-302. (PMID: 26414746) [Crossref]
31. Bagatir G, Kaya M, Suer I, Cefle K, Palanduz A, Palanduz S, et al. The effect of Anzer honey on X-ray induced genotoxicity in human lymphocytes: An in vitro study. Microsc Res Tech. 2022; 85: 2241-2250. (PMID: 35170166) [Crossref]
32. Kaya M, Suer I, Ozgur E, Capik O, Karatas OF, Ozturk S, et al. miR-145-5p suppresses cell proliferation by targeting IGF1R and NRAS genes in multiple myeloma cells. Turkish Journal of Biochemistry. 2023; 48: 563-569. [Crossref]

33. Suer I, Kaya M. Is the AURKB Gene Involved in Aml Cell Proliferation Since It is Targeted by miR-34a-5p and let-7b-5p? Konuralp Medical Journal. 2023; 15: 16-23. [Crossref]

34. Capik O, Sanli F, Kurt A, Ceylan O, Suer I, Kaya M, et al. CASC11 promotes aggressiveness of prostate cancer cells through miR-145/IGF1R axis. Prostate Cancer and Prostatic Dis. 2021; 24: 891-902. (PMID: 33753875) [Crossref]

35. Kaya M, Suer İ. The Effect of miR-34a-5p on Overexpressed AML Associated Genes. Journal of Istanbul Faculty of Medicine. 2023; 86: 59-68. [Crossref]

Original Article

Eur J Breast Health 2024; 20(4): 292-302
DOI: 10.4274/ejbh.galenos.2024.2024-7-1

Depression and Anxiety Symptoms Before and After Breast-Cancer Diagnosis Among Young Women in the Northern Finland Birth Cohort 1966

Anniina Tastula[1,2], Arja Jukkola[3,4], Anni-Emilia Alakokkare[1,2], Tanja Nordström[1,2,5], Peeter Karihtala[6], Jouko Miettunen[1,2], Sami Räsänen[7,8]

[1]Research Unit of Population Health, University of Oulu, Oulu, Finland
[2]Medical Research Center Oulu, Oulu University Hospital Oulu, Finland
[3]Department of Oncology of Medicine and Radiotherapy, Tampere University Hospital, Tampere, Finland
[4]Tampere University of Medicine and Health Sciences, Tampere Cancer Center, Tampere, Finland
[5]Northern Finland Birth Cohorts, Arctic Biobank, Infrastructure for Population Studies, Faculty of Medicine, University of Oulu, Oulu, Finland
[6]Department of Oncology, Helsinki University Hospital Comprehensive Cancer Center and University of Helsinki, Helsinki, Finland
[7]Department of Psychiatry, University of Oulu, Faculty of Medicine, Research Unit of Clinical Medicine, Oulu, Finland
[8]Department of Psychiatry, Oulu University Hospital, Oulu, Finland

ABSTRACT

Objective: The aim of the study was to explore depressive, anxiety, and mental-health related somatic symptoms among young breast-cancer survivors by considering symptoms before and after cancer onset.

Materials and Methods: The study sample included females from the prospective Northern Finland Birth Cohort 1966. Symptoms were assessed with the Hopkins Symptom Checklist-25 at the age of 31 and 46 years. We studied both subscales of depressive, anxiety, and somatic symptoms and single symptoms in secondary analyses.

Results: Thirty-one cases and 3.077 controls were included. Females diagnosed with breast cancer 3–8 years before the 46-year follow-up had increased depressive (p = 0.005) and somatic symptoms (p = 0.028) at the 46-year follow-up compared with the 31-year follow-up. This was not observed among those diagnosed <3 or >8 years before or among controls. Females diagnosed with breast cancer reported more lack of strength or energy compared with controls at the 46-year follow-up (p = 0.047). Among females who did not report feeling that the future is hopeless at the 31-year follow-up, significantly more females diagnosed with breast cancer reported this feeling at the 46-year follow-up compared with controls (p = 0.006).

Conclusion: Depressive and somatic symptoms increased significantly among young females at 3–8 years after breast-cancer diagnosis compared with the time before the cancer diagnosis. Psychosocial measures of support for breast-cancer survivors should be provided over the long-term.

Keywords: Breast cancer; depression; anxiety; young women

Cite this article as: Tastula A, Jukkola A, Alakokkare A-E, Nordström T, Karihtala P, Miettunen J, Räsänen S. Depression and Anxiety Symptoms Before and After Breast-Cancer Diagnosis Among Young Women in the Northern Finland Birth Cohort 1966. Eur J Breast Health. 2024; 20(4): 292-302

Key Points

- Depression and anxiety symptoms occurring before and after breast cancer diagnosis among young breast-cancer survivors are not well studied.
- At the post-diagnostic follow-up, depressive and mental-health related somatic symptoms increased significantly among those young breast-cancer survivors diagnosed 3–8 years before, while no differences were found among those diagnosed <3 or >8 years before or among controls.
- The occurrence of somatic symptoms during long-term follow-up of breast-cancer patients can be related to depression, which should be considered in clinical practice.
- More research is needed to assess how previous psychiatric symptoms of young breast-cancer survivors could help to identify and provide targeted psychosocial intervention for those who need it the most.

Corresponding Author:
Anniina Tastula; anniina.tastula@student.oulu.fi

Received: 10.07.2024
Accepted: 07.08.2024
Available Online Date: 26.09.2024

Introduction

Breast cancer in a women aged <50 years has a major impact at the individual and societal levels; many of these women tend to have a highly responsible role in the household as a provider and caretaker of young children, along with spouses. Furthermore, breast cancer may compromise their ability to work for an extended period and may even cause permanent household economic instability (1, 2). When compared with age-matched, cancer-free controls, the prevalence of both anxiety and depression symptoms is higher among breast-cancer survivors (3-5). Age at diagnosis seems to have a significant effect; younger breast-cancer survivors tend to more commonly report severe depressive or anxiety symptoms compared with older survivors (5-9). There is no universal definition of a young breast-cancer patient and the age limit generally varies between 40 to 50 years depending on the study (1, 2, 5, 6, 10). Previous psychiatric history can predict a more than 10-fold risk of post-diagnostic major depressive disorder among women who had surgery for breast cancer (11). In a prospective follow-up of 355 women (most aged between 51 to 64 years), major depression before breast-cancer diagnosis was associated with recurrence of depression during the first year after breast-cancer diagnosis. Similarly, generalized anxiety disorder (GAD) before breast cancer was associated with a recurrence of GAD (12). In the studies described above, data on mental health before breast-cancer diagnosis were assessed retrospectively (11, 12). To the best of our knowledge, only two studies prospectively collected data on mental health before breast-cancer diagnosis (8, 13), and only Kroenke et al. (8) explored a subgroup of young breast-cancer survivors. Thus, there is a knowledge gap on how previous psychiatric symptoms relate to mental health after breast-cancer diagnosis among young survivors.

We sought to evaluate how individual depression and anxiety symptoms occurring before breast cancer are related to corresponding symptoms after breast-cancer diagnosis. Using a large longitudinal cohort setting with a 15-year follow-up, we focused on breast cancer in young women, which is relatively rare. To our knowledge, this is the first prospective study where possible changes in individual psychiatric symptoms before and after breast-cancer diagnosis are explored among young breast-cancer survivors. We also analyzed change in somatic symptoms before and after breast-cancer diagnosis aggregated from the 25-item Hopkins Symptom Checklist (14).

Materials and Methods

Northern Finland Birth Cohort 1966

The Northern Finland Birth Cohort 1966 (NFBC1966) is a population-based epidemiologic study consisting of people who were expected to be delivered in the northernmost provinces of Finland in the year 1966 (15, 16). At baseline, 12.058 live-born children (5.890 girls and 6.168 boys) and their parents participated in the study, which represented 96.3% of births in the northernmost provinces (16). The data were collected prospectively using questionnaires and/or clinical examinations at the following timepoints: at birth and at 1, 14, 31, and 46 years of age. Our study used data collected on females at age 31 and 46 years. A detailed description of data collection is presented in Figure 1.

The NFBC 1966 31-year follow-up study was approved by the Ethical Committee of Oulu University Faculty of Medicine on 17 June 1996 and the 46-year study on 17 September 2012 (EETTMK 94/2011) by the Northern Ostrobothnia Hospital District Ethical Committee. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and all individuals have provided a written consent for participation in this study.

The Hopkins Symptom Checklist

The Hopkins Symptom Checklist (HSCL)-25 is a 25-item self-report screening instrument developed for detecting psychiatric symptoms among various patient groups in primary care (14). Based on a two-phased epidemiologic study, the HSCL-25 is suitable for screening psychiatric disorders, such as anxiety and mood disorders, with a sensitivity and specificity of 48% and 87%, respectively (17). In this questionnaire, individuals are asked to describe their symptoms from the preceding seven days on a scale from 1 to 4, where 1 refers to "Not at all", 2 "A little", 3 "Quite a bit", and 4 "Extremely". HSCL-25 can be divided into the following two separate subscales: 15 items regarding depression and 10 items regarding anxiety. The levels of depression or anxiety symptoms are determined by calculating the mean scores of items of each subscale. For this study, we also aggregated an additional subscale consisting of eight items describing mental health related-somatic symptoms. All these symptoms are associated with depression, anxiety, or both and almost all are included as diagnostic criteria (difficulties in falling asleep, poor appetite, lack of energy or strength, and low libido for depression and palpitation and trembling for anxiety disorders, respectively) (18). Although headache is not an official criteria for depression or anxiety, according to the International Classification of Diseases (ICD)-10 headache is associated with depression, anxiety, or both in multiple studies (19, 20). All items of the HSCL-25 are presented in Table 1. In addition, we formed dichotomous variables from each item, where 1 represented asymptomatic (0) and 2–4 represented symptomatic (1).

National Registries

Invasive breast cancer cases (C50.0–C50.9) were collected from the Care Register for Health Care (CRHC) administered by the National Institute for Health and Welfare (21) and registers of the Social Insurance Institution of Finland and the Finnish Center for Pensions

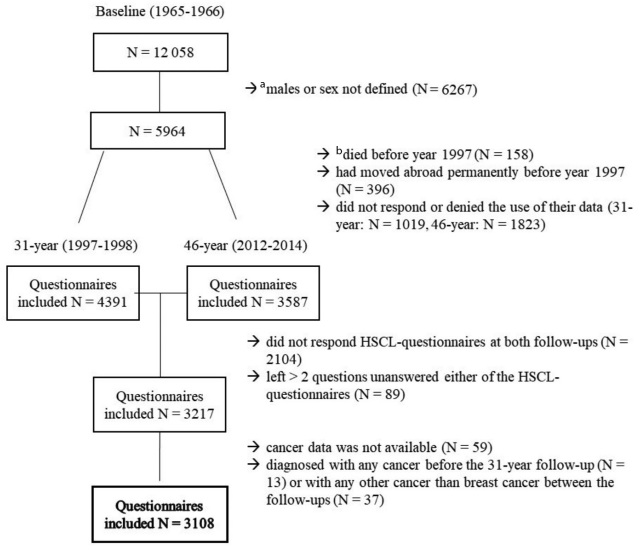

Figure 1. The selection of the study sample

HSCL: Hopkins symptom checklist

[a]: Live-births, 12.231 births overall

[b]: Stillborns also excluded, total = 173

based on the ICD-10 code. CRHC was preferred over the Finnish Cancer Registry due to the more recent update of cancer data (until the end of 2018). Data from national registers were linked to NFBC1966 using specific personal identification numbers.

Statistical Analysis

The exclusion process presented in Figure 1 was conducted prior to analysis. We chose to focus on female participants due to rarity of male breast cancer. Furthermore, we aimed to focus on breast cancer specifically so we excluded females diagnosed with other malignancies. We excluded females who left over 10% (>2 items) of HSCL unanswered. The analysis was conducted by comparing two groups, specifically individuals who were diagnosed with breast cancer between the follow-ups (BC group) and individuals who were not diagnosed with breast cancer between the follow-ups or who were not diagnosed with any cancer before the 31-year follow-up (controls). For primary analysis, Wilcoxon test was used to compare the subscale means (depression, anxiety, and somatic) between the 31-year and the 46-year follow-ups by forming the following subgroups of patients diagnosed with breast cancer: Patients diagnosed >8 years (the earliest BC group), 3–8 years (the middle BC group), and <3 years (the latest BC group) before the 46-year follow-up. For secondary analysis, we used cross-tabulation to review all 25 formed dichotomous variables separately at the 31-year and the 46-year follow-ups with Pearson's χ^2 test and Fisher's exact test, when appropriate. The obtained *p*-values were adjusted with Benjamini-Hochberg correction for multiple testing. Since one of our aims was to examine how a symptom occurred in the 46-year follow-up among individuals who did not have the symptom at the 31-year follow-up, we excluded individuals who had a reported symptom at the 31-year follow-up. Cells with a minimum frequency <5 were censored due to the Finnish legislation concerning patient data protection. The time period was determined by calculating the time from cancer diagnosis to date of completing the questionnaire form of the 46-year follow-up. Level of statistical significance was set to $p<0.05$ and all tests were two-tailed. Statistical analyses were performed using IBM SPSS Statistics, version 29.0 (IBM Corporation, Armonk, NY, USA).

Results

Overall, 3108 females were included for analysis and 31 (1.0%) were diagnosed with breast cancer between the 31-year and 46-year follow-ups according to national register data from 1997–2012. Mean ± SD age at breast-cancer diagnosis was 40.7±3.45 years. Nine of the patients were diagnosed during 1997–2004 (approximately between the ages of 31 and 38 years), 10 during 2005–2008 (between 39 and 42 years), and 12 during 2009–2012 (between 43 and 46) years. Thirteen individuals were diagnosed with any cancer before the 31-year follow-up and 37 individuals were first diagnosed with other malignancies (ductal carcinoma *in situ* not included) than breast cancer between the follow-ups and were excluded from the analysis (Figure 1). Less than five individuals were diagnosed with other malignancies (ductal carcinoma *in situ* not included) after breast cancer between the follow-ups; these individuals were excluded for other reasons based on the exclusion process. Among females who participated in the 31-year follow-up, 41 died before the 46-year follow-up; breast cancer was a cause of death for less than five females.

In the primary analysis, we examined how the mean scores of subscales differed between the follow-ups among groups (the earliest BC group, the middle BC group, the latest BC group, and controls). At the 46-year follow-up, the middle BC group had a significantly higher mean score for depression ($p = 0.0049$) and for somatic subscale ($p = 0.028$) compared with the 31-year follow-up. Other groups did not have significant differences between the follow-ups at any subscales. The results of Wilcoxon tests are presented in Table 2.

When depression and anxiety symptoms at both follow-ups were explored separately, the BC group more frequently reported lack of strength or energy at the 46-year follow-up compared with controls (71.0% and 53.1%, respectively; $p = 0.047$). The proportions were similar at the 31-year follow-up (61.3% and 58.8%, respectively; $p = 0.78$). Although the feeling that their whole life has been continuous exertion was more common among the BC group (51.6%) than among controls (36.9%) at the 46-year follow-up, the difference was not statistically significant ($p = 0.09$). All results of cross-tabulations

Table 1. Anxiety and depression subscales of Hopkins Symptom Checklist and somatic subscale created for this study

Anxiety	Depression	Somatic
1. Headache	2. Difficulties of falling asleep	1. Headache
4. Being strained or stressed	3. Feeling that the future is continuous	2. Difficulties of falling asleep
7. Episodes of panic or anxiety	5. Feeling lonely	11. Dizziness or a feeling of fainting
8. Such a strong feeling of restlessness that it has been difficult to sit still	6. Feeling that the whole life has been continuous exertion	13. Sexual interest missing or unable to enjoy sex
10. Being nervous and a feeling of restlessness	9. Feeling of worthlessness	14. Lack of strength or energy
11. Dizziness or a feeling of fainting	12. Worries	16. Trembling
16. Trembling	13. Sexual interest missing or unable to enjoy sex	17. Poor appetite
20. A sudden feeling of restlessness without a good reason	14. Lack of strength or energy	25. Palpitation
24. Anxiety	15. Suicidal thoughts	
25. Palpitation	17. Poor appetite	
	18. Crying easily	
	19. Feelings of being locked up or trapped	
	21. Self-reproach	
	22. Low spirits	
	23. Lack of interest	

Table 2. Results of Wilcoxon Single-Rank test for breast cancer groups

	The earliest BC group (n = 9) >8 years		The middle BC group (n = 10) 3-8 years		The latest BC group (n = 12) <3 years		Control group (n = 3077)	
Subscale	**Mean**	***p***	**Mean**	***p***	**Mean**	***p***	**Mean**	***p***
Anxiety 31-year	1.37	0.59	1.31	0.31	1.29	0.076	1.32	0.13
Anxiety 46-year	1.29		1.43		1.18		1.32	
Depression 31-year	1.39	0.95	1.36	0.0049*	1.27	0.86	1.38	0.68
Depression 46-year	1.38		1.63		1.29		1.39	
Somatic 31-year	1.50	0.91	1.34	0.028*	1.39	0.053	1.37	0.056
Somatic 46-year	1.51		1.53		1.27		1.39	

*: Statistical significance (p<0.05); BC: Breast cancer

of individual items of HSCL at both follow-ups are presented in Supplemental Table 1. In the secondary analysis, where all 25 items of HSCL were explored separately, among females who were asymptomatic at the 31-year follow-up, the feeling that the future is hopeless occurred more frequently among the BC group than controls at the 46-year follow-up (42.3% and 20.4%, respectively; p = 0.006). Although no statistically significant differences were found among individuals who were already symptomatic at the 31-year follow-up, most results were censored due to the low number of events. All results of cross-tabulations of individual items of HSCL are presented in Supplemental Table 2.

Discussion and Conclusion

To the best of our knowledge, this is the first study where prospectively assessed psychiatric symptoms before and after breast-cancer diagnosis were explored both individually and grouped into subscales. Our main finding was that individuals diagnosed with breast cancer 3–8 years before the 46-year follow-up reported significantly more symptoms of depression and mental-health related somatic symptoms than before the cancer diagnosis. Individuals diagnosed >8 years or <3 years before the 46-year follow-up had no significant changes in psychiatric symptoms. A large proportion of somatic subscale symptoms assessed in this study, such as headache, difficulties falling asleep, loss of sexual interest or inability to enjoy sex, lack of strength or energy, and poor appetite are related to depression (19, 20, 22) and these symptoms were also included in the depression subscale. This may explain why the means of both subscales were significantly higher among the middle BC group. The increase in symptoms among individuals diagnosed 3–8 years before assessing post-cancer symptoms may be explained by ongoing adjuvant treatment or long-term side effects of treatments, which may lead to experiencing more depressive and somatic symptoms. Our finding is consistent with findings from a prospective follow-up study of 164 women with breast cancer by Breidenbach et al. (23), where depression levels increased at 5 to 6 years post-diagnosis follow-up when compared with levels at 40 weeks post-diagnosis follow-up. Younger age (<50 years) was one of the predictors for depression at 5 to 6 years after diagnosis (23). An explanation for the finding that there was no increase in symptoms in the earliest BC group (where cancer was diagnosed >8 years previously) may be that they have lived the longest period after cancer diagnosis when participating in the 46-year follow-up. The tumor biology of earlier-onset breast cancer tends to be more aggressive, which increases the risk of recurrence and leads to poorer disease-free survival (24). This may explain why >8 years cancer-free time feels more secure and breast cancer would accordingly have less impact on mental health. However, the possibility of small-sample bias has to be considered due to relatively small subgroup sizes.

The latest BC group reported no significant changes in any psychiatric symptom subscales even though this group was diagnosed with breast cancer a relatively short time ago (within 3 years before the 46-year follow-up). In the short-term, there is a possibility of a well-being paradox, when becoming severely ill reshapes an individual's perception of health and priorities in life, such as the value of relationships and the ability to work (25). In addition, coping strategies, such as focusing on positivity amidst negativity, may be present (25, 26). Cancer treatments often require frequent hospital visits and check-ups, which may bring a sense of security during the treatment period. Therefore, transitioning from the treatment to follow-up period may give space for negative emotions regarding the cancer diagnosis. At least two earlier studies that used the Hospital Anxiety and Depression scale at pre-treatment and post-treatment follow-ups have shown that depressive and anxiety symptoms are highest at the diagnostic phase but are already decreasing by the treatment period (27, 28). Avis et al. (9) also reported that among women aged 24 to 54 years diagnosed with breast cancer, depressive symptom levels were highest at baseline but decreased during the follow-up of 24 months. However, the depressive symptom levels were higher compared to women aged ≥55 years (9). In the 20-year follow-up of the Women Health Initiative (WHI) observation study by Jones et al. (13), depressive symptoms increased, peaking at 1-year post-diagnosis compared with pre-diagnostic levels, and continued to be higher until after 10 years post-diagnosis, when the levels returned to pre-diagnosis levels.

When exploring all 25 items of HSCL individually, individuals diagnosed with breast cancer more often reported a lack of strength or energy compared with controls at the 46-year follow-up, which is consistent with previous studies of fatigue among breast-cancer patients (4, 29). This finding highlights that somatic symptoms, such as fatigue, should be considered as an important factor when evaluating the mental health of females diagnosed with breast cancer. Seventy-one percent who reported lack of strength or energy is a relatively high proportion, which further highlights the clinical importance of this symptom. However, this excess may also be explained by the

dichotomous variable setting, where a mild ("a little") experience of symptom is considered as a positive symptom. Nevertheless, these single question in this part of the HSCL cannot be considered as a straightforward comparison of cancer-related fatigue, which can be assessed using specific instruments (29, 30). Consistent with the life-threatening nature of breast cancer, when compared with individuals who did not have the feeling that the future is hopeless at the 31-year follow-up, significantly more individuals diagnosed with breast cancer reported this feeling at the 46-year follow-up compared with controls. As discussed above, breast cancers in younger women are usually more aggressive subtypes (24), and young breast-cancer survivors often experience the uncertainty of the future while having a crucial role not only as a caretaker but also being in a critical phase of career progression (31).

To the best of our knowledge, only two previous studies prospectively examined the mental health of women diagnosed with breast cancer (including the pre-diagnostic phase when there is no suspicion of cancer) (8, 13). Kroenke et al. (8) compared pre- and post-diagnostic levels of general mental health and revealed that general mental health declined more among survivors aged <40 years compared to older survivors. However, the status of mental health was not thoroughly explored (8). Jones et al. (13) examined levels of depressive symptoms at pre-diagnosis phase in the WHI observation study from 1993 to 2013. According to a systematic review, anxiety peaked after completing treatment among young breast-cancer survivors and in those who had previous mental health problems, but this also included the mental health status at baseline and was not limited to the pre-diagnosis period (32). Like our study, some of the previous studies did not specify the treatment types the patients received (13, 27) or the treatment types were not adjusted with the results (23, 28). The mean age of breast-cancer patients in the studies described above was 47.2 to 56.9 years (4, 27, 28, 33). However, the study of WHI was limited to postmenopausal women (mean age 62.7 years) (13). Similar to our study, none of the studies focused on prospectively assessed depression and anxiety symptoms before and after breast-cancer diagnosis specifically in younger breast-cancer patients.

Some limitations of the study should be acknowledged. Due to the small number of individuals diagnosed with breast cancer between the follow-ups, we were not able to interpret all results due to the requirement to ensure anonymity. The small sample size of breast-cancer survivors may lead to higher variability of reported results and further to bias. While most previous studies focused on disease-free survivors, the recurrence or treatment status of individuals with breast cancer at the 46-year follow-up was not known in this study. Survival bias may also be present as we excluded those who died between the follow-ups. Fewer than five individuals who died between the follow-ups had breast cancer as a cause of death. However, due to Finnish legislation, we were not able to classify which time period the deaths occurred in and if the individuals had breast-cancer diagnosis at the 31-year follow-up. We were also not able to adjust for possible confounders, such as characteristics of breast-cancer biological subtype, staging, administered treatments, or characteristics of an individual (age at diagnosis, marital status, family income, body mass index). When exploring somatic symptoms, we could not exclude those who had other somatic diseases besides breast cancer. However, this effect is likely very small, as Bekhuis et al. (22) did not find any chronic somatic diseases as a confounder while showing significant independent associations of multiple somatic symptom clusters among individuals with depression, anxiety disorders, or both. The HSCL questionnaire asks individuals to report symptoms during the past week, which may lead to recall bias. The somatic subscale of HSCL was aggregated empirically for this study to explore changes in reported somatic symptoms between the follow-ups and therefore have not been validated in a clinical arrangement. It is also important to acknowledge that many other factors such as childhood traumas and other adverse life-events, current financial, psychological and social burdens and different levels of mental resources may play a role in mental health of a female with breast-cancer diagnosis at the follow-ups. Although it was not possible to conduct due to small sample size in this study, these should be considered as potential confounders in future studies.

The study also has multiple strengths. This study used prospective and structured information on psychiatric symptoms collected in the pre-diagnosis period, particularly before suspicion of breast cancer, and compared these data to post-diagnosis data. HSCL is a reliable tool for comprehensive symptom assessment and screening of depression and anxiety disorders (17). The combination of a socioeconomically and demographically diverse population of NFBC1966 and universal healthcare allowed for conditions similar to real life, at least in high-income regions. Moreover, the amount of reported cancer cases is highly reliable due to the accurate registry data (34).

This study prospectively examined collected pre- and post-diagnosis psychiatric symptoms of young females diagnosed with breast cancer. To the best of our knowledge, such a study has not been conducted before. Individuals diagnosed >8 years or <3 years before the 46-year follow-up had no differences in anxiety, depression, or somatic symptom subscales of HSCL between the follow-ups, while individuals diagnosed 3–8 years before reported significantly more depression and somatic symptoms. The occurrence of somatic symptoms, such as headache, lack of strength or energy, lack of sexual interest, and poor appetite during long-term follow-up of breast-cancer patients may be related to depression, which should be considered as potential indicators of mental health problems and may be a way to identify and provide targeted psychosocial intervention for those who need it the most. Although we explored a broad selection of psychiatric symptoms prospectively before and after breast-cancer diagnosis, apart from the feeling that the future is hopeless, individual symptoms of HSCL reported before breast-cancer diagnosis did not significantly predict the psychiatric symptomatology at the post-diagnosis follow-up. However, most of the symptoms were censored due to the low event count. Therefore, more research with larger study populations is needed to assess how previous psychiatric symptoms of young breast-cancer survivors may play a role in their mental health after breast cancer.

Ethics Committee Approval: Study was approved by the Ethical Committee of Oulu University Faculty of Medicine on 17 June 1996 and the 46-year study on 17 September 2012 (EETTMK 94/2011) by the Northern Ostrobothnia Hospital District Ethical Committee.

Informed Consent: All individuals have provided a written consent for participation in this study.

Authorship Contributions

Concept: A.T., A.J., P.K., J.M., S.R.; Design: A.J., P.K., J.M., S.R.; Data Collection and/or Processing: A.T., A-E.A., T.N.; Analysis and/or Interpretation: A.T.; Literature Search: A.T.; Writing: A.T., A.J., A-E.A., T.N., P.K., J.M., S.R.

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

Financial Disclosure: A. Tastula's contribution to the study has been supported by a research grant of the Finnish Oncology Society in 2021 and Cancer Society of Northern Finland in 2024. Research grants awarded by these societies do not have identification numbers. NFBC1966 received financial support from the University of Oulu Grant no. 65354 and no. 24000692, Oulu University Hospital Grant no. 2/97, 8/97, and 24301140, Ministry of Health and Social Affairs Grant no. 23/251/97, 160/97, 190/97, National Institute for Health and Welfare, Helsinki Grant no. 54121, Regional Institute of Occupational Health, Oulu, Finland Grant no. 50621, 54231, and ERDF European Regional Development Fund Grant no. 539/2010 A31592.

References

1. Assogba ELF, Kamga AM, Costaz H, Jankowski C, Dumas A, Roignot P, et al. What Are Young Women Living Conditions after Breast Cancer? Health-Related Quality of Life, Sexual and Fertility Issues, Professional Reinsertion. Cancers (Basel). 2020; 12: 1564. (PMID: 32545701) [Crossref]
2. Ribi K, Pagan E, Sala I, Ruggeri M, Bianco N, Bucci EO, et al. Employment trajectories of young women with breast cancer: an ongoing prospective cohort study in Italy and Switzerland. J Cancer Surviv. 2023; 17: 1847-1858. (PMID: 35689003) [Crossref]
3. Doege D, Thong MSY, Koch-Gallenkamp L, Jansen L, Bertram H, Eberle A, et al. Age-specific prevalence and determinants of depression in long-term breast cancer survivors compared to female population controls. Cancer Med. 2020; 9: 8713-8721. (PMID: 33022889) [Crossref]
4. Williams AM, Khan CP, Heckler CE, Barton DL, Ontko M, Geer J, et al. Fatigue, anxiety, and quality of life in breast cancer patients compared to non-cancer controls: a nationwide longitudinal analysis. Breast Cancer Res Treat. 2021; 187: 275-285. (PMID: 33392843) [Crossref]
5. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. JNCI-J Natl Cancer I. 2012; 104: 386-405. (PMID: 22271773) [Crossref]
6. Champion VL, Wagner LI, Monahan PO, Daggy J, Smith L, Cohee A, et al. Comparison of younger and older breast cancer survivors and age-matched controls on specific and overall quality of life domains. Cancer. 2014; 120: 2237-2246. (PMID: 24891116) [Crossref]
7. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. BMJ. 2005; 330: 702. (PMID: 15695497) [Crossref]
8. Kroenke CH, Rosner B, Chen WY, Kawachi I, Golditz GA, Holmes MD. Functional Impact of Breast Cancer by Age at Diagnosis. J Clin Oncol. 2004; 22: 1849-1856. (PMID: 15143077) [Crossref]
9. Avis NE, Levine B, Naughton MJ, Case LD, Naftalis E, Van Zee KJ. Age-related longitudinal changes in depressive symptoms following breast cancer diagnosis and treatment. Breast Cancer Res Treat. 2013; 139: 199-206. (PMID: 23588951) [Crossref]
10. Fobair P, Stewart SL, Chang S, D'Onofrio C, Banks PJ, Bloom JR. Body image and sexual problems in young women with breast cancer. Psychooncology. 2006; 15: 579-594. (PMID: 16287197) [Crossref]
11. Qiu J, Yang M, Chen W, Gao X, Liu S, Shi S, et al. Prevalence and correlates of major depressive disorder in breast cancer survivors in Shanghai, China. Psycho-Oncol. 2012; 21: 1331-1337. (PMID: 21983854) [Crossref]
12. Hill J, Holcombe C, Clark L, Boothby MRK, Hincks A, Fisher J, et al. Predictors of onset of depression and anxiety in the year after diagnosis of breast cancer. Psychol Med. 2011; 41: 1429-1436. (PMID: 20942992) [Crossref]
13. Jones SMW, LaCroix AZ, Li W, Zaslavsky O, Wassertheil-Smoller S, Weitlauf J, et al. Depression and quality of life before and after breast cancer diagnosis in older women from the Women's Health Initiative. J Cancer Surviv. 2015; 9: 620-629. (PMID: 25708515) [Crossref]
14. 14. Derogatis LR, Lipman RS, Rickels K, Uhlenhuth HE, Covi L. The Hopkins Symptom Checklist (HSCL), A self-report symptom inventory. Syst. Res. 1974; 19: 1-15. (PMID: 4808738) [Crossref]
15. University of Oulu. Northern Finland Birth Cohort 1966. University of Oulu. (cited 2024 Jan 31) Available from: http://urn.fi/urn:nbn:fi:att:bc1e5408-980e-4a62-b899-43bec3755243. [Crossref]
16. Nordström T, Miettunen J, Auvinen J, Ala-Mursula L, Keinänen-Kiukaanniemi S, Veijola J, et al. Cohort Profile: 46 years of follow-up of the Northern Finland Birth Cohort 1966 (NFBC1966). Int J Epidemiol. 2022; 50: 1786-1787j. (PMID: 34999878) [Crossref]
17. Veijola J, Jokelainen J, Läksy K, Kantojärvi L, Kokkonen P, Järvelin M-R, et al. The Hopkins Symptom Checklist-25 in screening DSM-III-R axis-I disorders. Nord J Psychiatry. 2003; 57: 119-123. (PMID: 12745774) [Crossref]
18. World Health Organization. International Classification of Diseases and Related Health Problems. (10th ed.) World Health Organization. 1992. (cited 2024 Jan 31). Available from: https://icd.who.int/ [Crossref]
19. Carlehed G, Katz J, Nordin S. Somatic symptoms of anxiety and depression: A population-based study. Mental Health & Prevention. 2017; 6: 57-62. [Crossref]
20. Haug TT, Mykletun A, Dahl AA. The association between anxiety, depression, and somatic symptoms in a large population: the HUNT-II study. Psychosom Med. 2004; 66: 845-851. (PMID: 15564348) [Crossref]
21. Care Register for Health Care. Finnish Institute for Health and Welfare (THL), Finland. 2021. (updated 2023 Dec 7, cited 2024 Jan 31). Available from: https://thl.fi/en/web/thlfi-en/statistics-and-data/data-and-services/register-descriptions/care-register-for-health-care [Crossref]
22. Bekhuis E, Boschloo L, Rosmalen JGM, Schoevers RA. Differential associations of specific depressive and anxiety disorders with somatic symptoms. J Psychosom Res. 2015; 78: 116-122. (PMID: 25524436) [Crossref]
23. Breidenbach C, Heidkamp P, Hiltrop K, Pfaff H, Enders A, Ernstmann N, et al. Prevalence and determinants of anxiety and depression in long-term breast cancer survivors. BMC Psychiatry. 2022; 22: 101. (PMID: 35139815) [Crossref]
24. Zhu JW, Charkhchi P, Adekunte S, Akbari MR. What Is Known about Breast Cancer in Young Women? Cancers (Basel). 2023; 15: 1917. (PMID: 36980802) [Crossref]
25. Cuthbert CA, Farragher JF, Farrer CL, Cheung WY. Living with paradox: A qualitative study of colorectal cancer patients' experiences in managing their health after cancer treatment. Eur J Cancer Care (Engl). 2021; 30: e13416. (PMID: 33506569) [Crossref]
26. Drageset S, Lindstrøm TC, Underlid K. "I just have to move on": Women's coping experiences and reflections following their first year after primary breast cancer surgery. Eur J Oncol Nurs. 2016; 21: 205-211. (PMID: 26521054) [Crossref]
27. Izci F, Ozdem G, Ilgun AS, Agacayak F, Duymaz T, Erdogan Z, et al. Pre-Treatment and Post-Treatment Anxiety, Depression, Sleep and Sexual Function Levels in Patients with Breast Cancer. Eur J Breast Health. 2020; 16: 219-225. (PMID: 32656524) [Crossref]
28. Vahdaninia M, Omidvari S, Montazeri A. What do predict anxiety and depression in breast cancer patients? A follow-up study. Soc Psych Psychiatr Epidemiol. 2009; 45: 355-361. (PMID: 19458878) [Crossref]
29. Maass SWMC, Brandenbarg D, Boerman LM, Verhaak PFM, Bock GH de, Berendsen AJ. Fatigue among Long-Term Breast Cancer Survivors:

A Controlled Cross-Sectional Study. Cancers. 2021; 13: 1301. (PMID: 33803966) [Crossref]

30. Kim SH, Son BH, Hwang SY, Han W, Yang J-H, Lee S, et al. Fatigue and depression in disease-free breast cancer survivors: prevalence, correlates, and association with quality of life. J Pain Symptom Manage. 2008; 35: 644-655. (PMID: 18358687) [Crossref]
31. Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of Life in Long-Term, Disease-Free Survivors of Breast Cancer: a Follow-up Study. JNCI-J J Natl Cancer Inst. 2002; 94: 39-49. (PMID: 11773281) [Crossref]
32. Harris J, Cornelius V, Ream E, Cheevers K, Armes J. Anxiety after completion of treatment for early-stage breast cancer: a systematic review to identify candidate predictors and evaluate multivariable model development. Support Care Cancer. 2017; 25: 2321-2333. (PMID: 28405845) [Crossref]
33. Hopwood P, Sumo G, Mills J, Haviland J, Bliss JM. START Trials Management Group. The course of anxiety and depression over 5 years of follow-up and risk factors in women with early breast cancer: results from the UK Standardisation of Radiotherapy Trials (START). Breast. 2010; 19: 84-91. (PMID: 20042336) [Crossref]
34. Pukkala E, Engholm G, Højsgaard Schmidt LK, Storm H, Khan S, Lambe M, et al. Nordic Cancer Registries - an overview of their procedures and data comparability. Acta Oncol. 2018; 57: 440-455. (PMID: 29226751) [Crossref]

Supplemental Table 1. Symptoms of Hopkins Symptom Checklist (HSCL) at the 31-year and the 46-year follow-ups

	Follow-up	Asymptomatic (1 = not at all)		Symptomatic (2 = a little bit, 3 = quite a bit, 4 = extremely)		Comparison between symptomatic and asymptomatic stratified by BC status
HSCL symptoms		**Controls, *n* (%)**	**Individuals with BC, *n* (%)**	**Controls, *n* (%)**	**Individuals with BC, *n* (%)**	***p***
1. Headache (A, S)	31-y	1181 (38.5)	9 (29.0)	1887 (61.5)	22 (71.0)	0.28
	46-y	1307 (42.6)	10 (32.3)	1760 (57.4)	21 (67.7)	0.25
2. Difficulties in falling asleep (D, S)	31-y	2073 (67.4)	22 (71.0)	1002 (32.6)	9 (29.0)	0.67
	46-y	1890 (61.6)	18 (58.1)	1178 (38.4)	13 (41.9)	0.69
3. Feeling that the future is hopeless (D)	31-y	2229 (72.6)	26 (83.9)	841 (27.4)	5 (16.1)	0.16
	46-y	2222 (72.5)	19 (61.3)	844 (27.5)	12 (38.7)	0.17
4. Being strained or stressed (A)	31-y	1015 (33.1)	6 (19.4)	2056 (66.9)	25 (80.6)	0.11
	46-y	1048 (34.2)	10 (32.3)	2020 (65.8)	21 (67.7)	0.82
5. Feeling lonely (D)	31-y	2192 (71.2)	≥27 (≥87.1)	885 (28.8)	<5 (<12.9)	**
	46-y	2205 (71.9)	24 (77.4)	860 (28.1)	7 (22.6)	0.50
6. Feeling that the whole life has been continuous exertion (D)	31-y	2113 (68.8)	21 (70.0)	960 (31.2)	9 (30.0)	0.88
	46-y	1941 (63.1)	15 (48.4)	1133 (36.9)	16 (51.6)	0.090
7. Episodes of panic or anxiety (A)	31-y	2603 (84.7)	≥27 (≥87.1)	469 (15.3)	<5 (<12.9)	**
	46-y	2629 (85.8)	25 (80.6)	434 (14.2)	6 (19.4)	0.43[a]
8. Such a strong feeling of restlessness that it has been difficult to sit still (A)	31-y	2713 (88.3)	≥27 (≥87.1)	361 (11.7)	<5 (<12.9)	**
	46-y	2766 (90.0)	≥27 (≥87.1)	309 (10.0)	<5 (<12.9)	**
9. Feeling of worthlessness (D)	31-y	2288 (74.5)	24 (77.4)	782 (25.5)	7 (22.6)	0.71
	46-y	2270 (73.9)	24 (77.4)	803 (26.1)	7 (22.6)	0.65
10. Being nervous and a feeling of restlessness (A)	31-y	1680 (54.8)	13 (41.9)	1384 (45.2)	18 (58.1)	0.15
	46-y	1940 (63.2)	21 (67.7)	1129 (36.8)	10 (32.3)	0.60
11. Dizziness or a feeling of fainting (A, S)	31-y	2433 (79.1)	23 (74.2)	643 (20.9)	8 (25.8)	0.51
	46-y	2454 (79.9)	≥27 (≥87.1)	618 (20.1)	<5 (<12.9)	**
12. Worries (D)	31-y	877 (28.6)	8 (25.8)	2191 (71.4)	23 (74.2)	0.73
	46-y	1011 (32.9)	8 (25.8)	2064 (67.1)	23 (74.2)	0.40
13. Sexual interest missing or unable to enjoy sex (D, S)	31-y	1768 (57.5)	19 (61.3)	1306 (42.5)	12 (38.7)	0.67
	46-y	1835 (59.8)	16 (51.6)	1233 (40.2)	15 (48.4)	0.35
14. Lack of strength or energy (D, S)	31-y	1268 (41.2)	12 (38.7)	1807 (58.8)	19 (61.3)	0.78
	46-y	1440 (46.9)	9 (29.0)	1630 (53.1)	22 (71.0)	0.047*
15. Suicidal thoughts (D)	31-y	2984 (97.0)	≥27 (≥87.1)	93 (3.0)	<5 (<12.9)	**
	46-y	2955 (96.1)	≥27 (≥87.1)	119 (3.9)	<5 (<12.9)	**
16. Trembling (A, S)	31-y	2933 (95.3)	31 (100)	144 (4.7)	0 (0)	0.40[ab]
	46-y	2912 (94.8)	≥27 (≥87.1)	161 (5.2)	<5 (<12.9)	**
17. Poor appetite (D, S)	31-y	2795 (90.9)	25 (80.6)	281 (9.1)	6 (19.4)	0.060[a]
	46-y	2821 (91.9)	≥27 (87.1)	249 (8.1)	<5 (<12.9)	**
18. Crying easily (D)	31-y	2137 (69.5)	22 (71.0)	937 (30.5)	9 (29.0)	0.86
	46-y	2287 (74.6)	22 (71.0)	780 (25.4)	9 (29.0)	0.65

Supplemental Table 1. Continued

	Follow-up	Asymptomatic (1 = not at all)		Symptomatic (2 = a little bit, 3 = quite a bit, 4 = extremely)		Comparison between symptomatic and asymptomatic stratified by BC status
HSCL symptoms		**Controls, *n* (%)**	**Individuals with BC, *n* (%)**	**Controls, *n* (%)**	**Individuals with BC, *n* (%)**	***p***
19. Feelings of being locked up or trapped (D)	31-y	2863 (93.1)	≥27 (≥87.1)	212 (6.9)	<5 (<12.9)	**
	46-y	2924 (95.2)	31 (100)	147 (4.8)	0 (0)	0.40[ab]
20. A sudden feeling of restlessness without a good reason (A)	31-y	2701 (87.8)	≥27 (≥87.1)	375 (12.2)	<5 (<12.9)	**
	46-y	2748 (89.4)	≥27 (≥87.1)	325 (10.6)	<5 (<12.9)	**
21. Self-reproach (D)	31-y	2318 (75.4)	25 (80.6)	757 (24.6)	6 (19.4)	0.50
	46-y	2368 (77.0)	23 (74.2)	706 (23.0)	8 (25.8)	0.71
22. Low spirits (D)	31-y	1783 (58.0)	18 (58.1)	1290 (42.0)	13 (41.9)	1.00
	46-y	1847 (60.1)	20 (64.5)	1227 (39.9)	11 (35.5)	0.62
23. Lack of interest (D)	31-y	1954 (63.5)	19 (61.3)	1121 (36.5)	12 (38.7)	0.80
	46-y	1971 (64.2)	19 (61.3)	1100 (35.8)	12 (38.7)	0.74
24. Anxiety (A)	31-y	2609 (84.8)	31 (100)	466 (15.2)	0 (0)	0.010*[ab]
	46-y	2612 (85.4)	25 (80.6)	448 (14.6)	6 (19.4)	0.44[a]
25. Palpitation (A, S)	31-y	2565 (83.4)	26 (83.9)	511 (16.6)	5 (16.1)	0.94
	46-y	2330 (76.3)	≥27 (≥87.1)	725 (23.7)	<5 (<12.9)	**

[a]: More than 20% of cells in this subtable have expected cell counts less than 5 and Fisher's test is conducted.

[b]: The minimum expected cell count in this subtable is less than one.

*: Statistical significancy (p<0.05, Benjamini-Hochberg)

**: p-value is censored due to cell count being less than five, non-cancer controls total = 3071 and individuals with breast cancer (BC) total = 31. A = A symptom of anxiety subscale, D = a symptom of depression subscale and S = a symptom of somatic subscale

Supplemental Table 2. Symptoms of Hopkins Symptom Checklist (HSCL) occurring at the 46-year follow-up among individuals diagnosed for breast cancer (BC group) and non-cancer controls

		Did not have the symptom at the 31-year follow-up			Had the symptom at the 31-year follow-up		
HSCL symptoms	**Group**	**Total, *n***	**Occurs at the 46-year follow-up, *n* (%)**	***p***	**Total, *n***	**Occured at the 46-year follow-up, *n* (%)**	***p***
1. Headache (A, S)	Controls	1180	493 (41.7)	**	1878	1264 (67.0)	0.93
	BC group	9	≥5 (≥55.6)		22	15 (68.2)	
2. Difficulties in falling asleep (D, S)	Controls	2067	654 (31.5)	0.99	999	522 (52.1)	**
	BC group	22	7 (31.8)		9	≥5 (≥55.6)	
3. Feeling that the future is hopeless (D)	Controls	2222	454 (20.4)	0.0062*			
	BC group	26	11 (42.3)				
4. Being strained or stressed (A)	Controls				2048	1493 (72.6)	0.73
	BC group				25	19 (76.0)	
5. Feeling lonely (D)	Controls	2184	456 (20.8)	0.94			
	BC group	28	6 (21.4)				
6. Feeling that the whole life has been continuous exertion (D)	Controls	2111	590 (27.9)	0.30	959	542 (56.5)	**
	BC group	21	8 (38.1)		9	≥5 (≥55.6)	
7. Episodes of panic or anxiety (A)	Controls	2593	293 (11.3)	0.13[a]			
	BC group	29	6 (20.7)				
8. Such a strong feeling of restlessness that it has been difficult to sit still (A)	Controls	2711	202 (7.4)	**			
	BC group	29	<5 (<13.8)				
9. Feeling of worthlessness (D)	Controls	2285	444 (19.4)	**			
	BC group	24	<5 (<20.8)				
10. Being nervous and a feeling of restlessness (A)	Controls	1674	425 (25.3)	**	1382	699 (50.5)	0.61
	BC group	13	<5 (<30.8)		18	8 (44.4)	
11. Dizziness or a feeling of fainting (A, S)	Controls	2430	390 (16.0)	**			
	BC group	23	<5 (<17.4)				
12. Worries (D)	Controls	877	424 (48.3)	**	2189	1634 (74.6)	0.94
	BC group	8	≥5 (≥62.5)		23	17 (73.9)	
13. Sexual interest missing or unable to enjoy sex (D, S)	Controls	1761	559 (31.6)	0.64	1304	673 (51.5)	**
	BC group	19	7 (36.8)		12	≥8 (≥66.7)	
14. Lack of strength or energy (D, S)	Controls	1262	484 (38.2)	**	1806	1145 (63.4)	0.35
	BC group	12	≥8 (≥66.7)		19	14 (73.7)	
15. Suicidal thoughts (D)	Controls	2981	95 (3.2)	1.00 [ab]			
	BC group	30	0 (0)				
16. Trembling (A, S)	Controls	2929	125 (4.3)	**			
	BC group	31	<5 (<12.9)				
17. Poor appetite (D, S)	Controls	2788	194 (6.9)	**	281	55 (19.6)	0.60[ab]
	BC group	25	<5 (<16.0)		6	0 (0)	
18. Crying easily (D)	Controls	2130	417 (19.5)	0.17[a]	934	362 (38.6)	**
	BC group	22	7 (31.8)		9	<5 (<44.4)	
19. Feelings of being locked up or trapped (D)	Controls	2858	113 (3.9)	0.63[a]			
	BC group	30	0 (0)				

Supplemental Table 2. Continued

		Did not have the symptom at the 31-year follow-up			Had the symptom at the 31-year follow-up		
HSCL symptoms	**Group**	**Total, *n***	**Occurs at the 46-year follow-up, *n* (%)**	**p**	**Total, *n***	**Occured at the 46-year follow-up, *n* (%)**	**p**
20. A sudden feeling of restlessness without a good reason (A)	Controls	2697	212 (7.8)	**			
	BC group	27	<5 (<14.8)				
21. Self-reproach (D)	Controls	2315	395 (17.0)	**			
	BC group	25	<5 (<16.0)				
22. Low spirits (D)	Controls	1781	494 (27.7)	1.00[a]	1289	732 (56.7)	0.44
	BC group	18	5 (27.8)		13	6 (46.2)	
23. Lack of interest (D)	Controls	1950	513 (26.3)	0.30	1119	585 (52.2)	0.46
	BC group	19	7 (36.8)		12	5 (41.7)	
24. Anxiety (A)	Controls	2593	287 (11.0)	0.15[a]			
	BC group	31	6 (19.4)				
25. Palpitation (A, S)	Controls	2547	519 (20.2)	**			
	BC group	26	<5 (<15.4)				

[a]: More than 20% of cells in this subtable have expected cell counts less than 5 and Fisher's test is conducted.

[b]: The minimum expected cell count in this subtable is less than one.

*: Statistical significancy (p<0.05, Benjamini-Hochberg)

**: p-value is censored due to cell count being less than five, non-cancer controls total = 3071 and individuals with breast cancer (BC) total = 31.

A = A symptom of anxiety subscale, D = a symptom of depression subscale and S = a symptom of somatic subscale

Original Article

Eur J Breast Health 2024; 20(4): 303-308
DOI: 10.4274/ejbh.galenos.2024.2024-6-2

Effect of Flaxseed on Pain Relief and Quality of Life in Patients With Mastalgia: A Single Arm Interventional Study

Tabish Ansari, Priyanka Rai, Amarjot Singh, Rohit Srivastava, Sunil Singh, Vaibhav Raj Gopal
Department of General Surgery, Dr. Ram Manohar Lohia Institute of Medical Sciences, Uttar Pradesh, India

ABSTRACT

Objective: Mastalgia, a common complaint among women, denotes breast discomfort that can manifest as cyclical or non-cyclical. Reassurance, mechanical support and various non-pharmacological treatments, like flaxseeds, have been seen to have a good effect in treating mastalgia. Thus, the aim of this study was to investigates the efficacy of flaxseed in alleviating pain associated with mastalgia and its impact on the overall health-related quality of life among female patients.

Materials and Methods: Conducted at a tertiary care center in Northern India over 18 months, it employed a single-arm interventional design. The participants included females aged 18 years and older presenting with breast pain at the Department of General Surgery. The intervention involved daily consumption of 30 g of milled flaxseed for each participant, administered over a period of six months. Pain severity was assessed using the visual analogue scale (VAS) before supplementation and at follow-up intervals up to six months. Concurrently, the Short Form-12 (SF-12) items Health Survey measured health-related quality of life, encompassing both physical and mental health domains. Statistical analysis employed parametric (paired t-test) and non-parametric tests (chi-square, McNemar) where appropriate, with statistical significance set at $p<0.05$.

Results: Two hundred women with mastalgia were included with a significant reduction in mean VAS scores from 6.03±0.83 at baseline to 2.19±0.66 at six months post-intervention ($p = 0.0001$). This reduction in pain intensity demonstrated a positive correlation with duration of flaxseed supplementation, notably declining after the initial three months. The mean difference in physical and mental SF-12 score at first visit and at 6 months after intervention was significant ($p = 0.0001$).

Conclusion: This study underscores the potential of flaxseed as a therapeutic option for managing mastalgia and enhancing health-related quality of life among affected individuals.

Keywords: Flaxseed; mastalgia; pain measurement; quality of life; SF-12

Cite this article as: Ansari T, Rai P, Singh A, Srivastava R, Singh S, Gopal VR. Effect of Flaxseed on Pain Relief and Quality of Life in Patients With Mastalgia: A Single Arm Interventional Study. Eur J Breast Health. Eur J Breast Health. 2024; 20(4): 303-308

Key Points

- Mastalgia, a common complaint among women, denotes breast discomfort that can manifest as cyclic or non-cyclic. Reassurance, mechanical support and various non-pharmacological treatments like flaxseeds have been seen to have a good effect in treating mastalgia. So, the aim of this study was to investigates the efficacy of flaxseed in alleviating pain associated with mastalgia and its impact on the overall health-related quality of life among female patients.

Introduction

Mastalgia, a common complaint among women, is the term used to describe breast discomfort. Mastalgia may be cyclical or non-cyclical (1). While the exact etiology of mastalgia remains multifactorial and often elusive, hormonal fluctuations, particularly in relation to the menstrual cycle, are frequently implicated. Furthermore, lifestyle factors, such as stress, caffeine intake, and diet have been suggested as potential contributors to its prevalence (2). The complex interplay of physiological, psychological, and environmental factors underscores the need for tailored approaches in understanding and managing this prevalent breast-related symptomatology (3).

Reassurance, mechanical support and various non-pharmacological treatments, like flaxseeds, have been seen to have a good effect in treating mastalgia (4, 5). The seeds of flax (*Linum usitatissimum*) have garnered attention for their potential impact on various aspects of human health. Rich in alpha-linolenic acid (ALA), a plant-based omega-3 fatty acid, flax seeds have been associated with cardiovascular benefits, such as a reduction in blood pressure and improvement in lipid profiles (6). In addition, the lignans present in flax seeds, particularly secoisolariciresinol diglucoside, exhibit antioxidant properties and may contribute to anti-inflammatory effects within the body (7). The soluble fibre content of flax seeds, primarily in the form of mucilage

Corresponding Author:
Priyanka Rai; drpriyanka.rai27@gmail.com

Received: 16.06.2024
Accepted: 20.08.2024
Available Online Date: 26.09.2024

gums, has been linked to gastrointestinal health by promoting regular bowel movements and potentially mitigating constipation (7, 8). Thus there is evidence that flaxseed helps in overall improvement in quality of life of an individual. There is a paucity of literature concerning the use of flaxseed for treating mastalgia and its effect on overall health. Therefore, the aim of this study was to measure the effect of flaxseed in reducing pain in mastalgia and the role of daily flaxseed intake in overall health related quality of life in patients with mastalgia.

Materials and Methods

Study Design and Setting

This was a **s**ingle arm, interventional study conducted at the Department of General Surgery of a tertiary care centre in Northern India over a period of 18 months.

Study Participants

Any female patient, aged 18 years or above, coming to the Department of General Surgery with breast pain was eligible as a subject for this study. Those who were pregnant, who had not yet achieved menarche, skipped medication for three consecutive days or five periodic days, or with a history of breast cancer or congenital anomalies were excluded from the study. Those unwilling to participate were also excluded from the study.

Sample Size: For the purpose of sample size estimation, two studies were used (9). The sample size formula used was:

$X= (Z_{1-a/2 +} Z_{1-\beta}) * 2\ \sigma^2/d^2$,

$Z_{1-a/2}$ – critical value of the normal distribution at a/2 (for a confidence level of 95%, a = 0.05 and the critical value was 1.96.

$Z_{1-\beta}$ - critical value of the normal distribution at β (for power of 80%, β = 0.2 and the critical value was 0.84.

σ^2- Pooled variance calculated using the change in mean visual analogue scale (VAS) score before and after taking flaxseed (value was 1.25).

d- hypothesized difference (difference in the mean in the intervention group from baseline) (value was 0.6) (9).

To detect a hypothesized difference of 0.6 units in the outcome measure, at 80% power and 95% confidence interval, the required minimum sample size was 171. Taking an estimated 10% drop out rate, the final sample size was a minimum of 188 patients.

Study Procedure

Any female patient presenting with the complaint of breast pain and aged over 18 years was eligible. After applying exclusion criteria the remaining women were instructed in the use of the VAS, and written and informed consent was obtained. After that a detailed history was taken, including breast pain history, followed by a thorough physical examination. Investigations, such as breast ultrasonography (USG) including axilla USG if indicated, mammography and fine needle aspiration cytology was advised as per patient's symptoms andsigns.

Mechanical support and reassurance were given to all the patients by counselling her that symptoms are not associated with any major or serious breast conditions, especially cancer. Reassurance was also supported by normal findings on investigation. Each woman received 30 g of milled flaxseed, which was taken with a glass of water, juice, milk, soup or yogurt daily. Severity of pain was assessed before supplementation of flaxseed and every follow-up up to 6 months after starting supplementation of flaxseed.

Flaxseed used in this study was milled and consumed by dissolving it into a glass of water using a tablespoon (1 tbs~15g x2) per day. It should be noted that we did not measure the composition of the flaxseed used in our study. Instead, we obtained this information from the literature. A measure of 10 g ground flaxseed supplement was reported to provide approximately 50 kcal, 2.4 g of protein, 3.6 g of fat (50–60% α- linolenicacid), 2.4 g of carbohydrate, and 2.2 g of dietary fibre (including 1.2 g of soluble fibre) (8). Each of these measures should be increased three-fold for the daily doses received by the participants in ous study.

Tablet Paracetamol 650 mg was given for patient on SOS if the pain was of severe intensity. Quantity of tablet Paracetamol consumed was noted.

Health-related quality of life was measured using the The Short Form-12 (SF-12) Health Survey. SF-12 items Health Survey is a condensed version of the Short Form-36 (SF-36) items Health Survey, designed to gauge an individual's subjective perception of health as biopsychosocial well-being. The SF-12 addresses various aspects of physical health (e.g., "Have you experienced difficulties, such as climbing flights of stairs, in your work or daily activities due to your physical health?") and mental health (e.g., "Have you felt down-hearted and blue?"). The overall scores generate a physical health index (PSF-12) and a mental health index (MSF-12), with lower scores indicating higher levels of disability. In the current sample, both subscales demonstrated adequate internal consistency (PSF-12: ω = 0.80; MSF-12: ω = 0.85) (10).

A predesigned proforma, especially designed for this study, was used to record relevant information for each individual patient.

Statistical Analysis

The effect of flaxseed was defined by either a reduction in the severity of pain to lower pain or a decrease in pain duration (days) based upon the VAS scale. In the statistical analysis, parametric or non-parametric tests were used, as appropriate. The parametric tests used was the paired sample t-test and the non-parametric test was chi-square and the McNemar test. A value of p<0.05 was considered to be statistically significant. R statistical software, version 4.2.1 used for statistical analysis.

Informed consent was obtained from all the participants. Ethical approval for the study was obtained from the Dr. Ram Manohar Lohia Institute of Medical Sciences Ethical Committee (approval number: 96/22, date: 15.09.2022). Confidentiality in respect of participating patients was maintained.

Results

A total of 200 women with mastalgia were treated with flaxseed. The mean age of the study population was 34.3±4.7 years. Most of the study participants lived in urban areas (70.5%), a quarter were illiterate (25.5%) followed by intermediate level of education (23%). Moreover, 60% were unemployed and 90.5% were married. Most of the study participants were of lower middle socio-economic status (28%) followed by middle socioeconomic status (22.5%). Of 200

patients, 104 (52%) were in the normal weight body mass index (BMI) category 18.5–24.9 kg/m^2 (Table 1).

Most of the study participants were multiparous (94%) and 93% had breastfed their babies. With respect to menstrual history, 82.5% had normal bleeding, 85% had normal regularity and 73% were painless (Table 2). The mean VAS score at first visit was 6.03±0.83. At one month after flaxseed administration mean VAS was 4.00±0.79 and at three and six months after flax seed administration, VAS was 2.72±0.63 and 2.19±0.66, respectively. This difference in mean VAS scores at various intervals was significant (p = 0.0001) (Table 3).

Table 1. Baseline characteristics of the study participants (n = 200)

Variable		*n*	%
Residence	**Rural**	59	29.5%
	Urban	141	70.5%
Education	**Illiterate**	51	25.5%
	Primary	41	20.5%
	Secondary	30	15%
	Intermediate	46	23%
	Graduate and above	32	16%
Employment	**Employed**	78	39%
	Unemployed	122	61%
Marital status	**Married**	181	90.5%
	Unmarried	19	9.5%
Socioeconomic status	**Lower**	42	21%
	Lower middle	56	28%
	Middle	45	22.5%
	Upper middle	31	15.5%
	Upper	26	13%
Body mass index	**<18.5 kg/m^2**	11	5.5%
	18.5–24.9 kg/m^2	104	52%
	25–29.9 kg/m^2	76	38%
	>30 kg/m^2	9	4.5%

Table 2. Distribution of study participants on the basis of menstrual and birth history

Variable		*n*	%
Parity	**Nulliparous**	12	6.0%
	Multiparous	188	94.0%
Breast feeding	**No**	14	7%
	Yes	186	93%
Menstrual bleeding	**Scanty**	8	4%
	Normal	165	82.5%
	Heavy	27	13.5%
Menstrual regularity	**Polymenorrhea**	8	4%
	Normal	170	85%
	Oligomenorrhea	22	11%
Pain during or before menstruation	**Painless**	146	73.0%
	Painful	54	27.0%

The mean difference of VAS score from baseline to one month after flax seed administration was 2.03±0.78. This difference in mean VAS score had a positive and strong correlation (r = 0.646; p = 0.0001). The mean difference of VAS score from first visit to 3 months after flax seed administration was 3.31±0.96. This difference in mean VAS score had a moderate positive correlation (r = 0.542; p = 0.0001) The mean difference in VAS score from first visit to six months was 4.120.95±, again with a moderate positive correlation (r = 0.565; p = 0.0001) (Table 4).

Changes in mean VAS scores among the 200 women with mastalgia, categorized by BMI grouping (underweight, normal, overweight and obese) were compared (Table 5). At the first visit, mean VAS scores were slightly higher in participants with higher BMI, but the differences were not significant. At three months, pain levels decreased across all BMI categories, with higher BMI groups still reporting slightly higher pain, yet without significant differences between the groups. By six months, pain reduction was sustained, and VAS scores were similar across all BMI groups, showing no significant differences. Overall, pain levels decreased over time regardless of BMI, indicating that BMI did not significantly influence the change in pain levels. The mean improvement in physical and mental SF-12 score at first visit and at six months after intervention was significant (Table 6).

Discussion and Conclusion

Our study prospectively assessed women with mastalgia and advised intake of 30 g of flaxseed daily for six months to assess its role in relieving mastalgia. During the study period 74 females with mastalgia with no underlying cause were enrolled.

The mean age of women in our cohort with mastalgia was 34.3±4.7 years which was similar to the age reported by Fakhravar et al. (11), and Mohammed (12), in their studies, suggesting that the most

Table 3. Descriptive statistics VAS score of study participants at first visit and at follow-up after intervention

Visual analogue scale	Mean ± standard deviation	Greenhouse geisser value	*p*
First visit	6.03±0.83	0.613	**0.0001**
1 month	4.00±0.79		
3 months	2.72±0.63		
6 months	2.19±0.66		

Table 4. Change in VAS at various follow-up from baseline

VAS	Mean difference ± standard deviation	Correlation coefficient *(r)*	*t*-value	*p*
VAS First visit & VAS 1 month	2.03±0.78	0.646	9.480	**0.0001**
VAS First visit & VAS 3 month	3.31±0.96	0.542	22.474	**0.0001**
VAS First visit & VAS 6 month	4.12±0.95	0.565	21.726	**0.0001**

VAS: Visual analogue scale

Table 5. Change in mean VAS at each follow-up based on the BMI of the study participants

VAS	BMI (kg/m²)				*p*
	<18.5	18.5–24.9	25–29.9	≥30	
First visit	6.01±0.27	6.11±0.21	6.32±0.56	6.66±0.41	0.414
3 months	2.45±0.13	2.96±0.71	3.61±0.84	3.74±1.01	0.312
6 months	2.11±0.49	2.28±0.68	2.35±0.77	2.37±0.61	0.992

VAS: Visual analogue scale; BMI: Body mass index

Table 6. Effect of flaxseed on overall quality of life of study participants

SF-12 score	First visit	After 6 months of treatment	*p*
Physical SF-12 score	56.03±15.83	83.36±7.61	0.0001
Mental SF-12 score	64.71±11.79	84.27±5.32	0.0001

SF-12: Short Form-12

common occurrence of mastalgia was seen around 35 years of age and this was statistically significant. Moreover, the majority of the patients with mastalgia in our cohort were married and this was in agreement with Fakhravar et al. (11) and Sunil Krishna and Shenoy (13).

Flax is notable as a major source of lignans, one of the phytoestrogens. Lignans can act as both agonists and antagonists to estrogen and also have antioxidant properties. As a result, flaxseed and its lignans can produce strong anti-estrogenic effects on estrogen receptors (14). In addition, flaxseed is rich in other phytoestrogens, which are effective in reducing symptoms of premenstrual syndrome, such as headaches and premenstrual breast tenderness (15). Research by Goss et al. (16) found that consuming 25 g of flaxseed daily significantly alleviates cyclical breast pain. Similarly, Rosolowich et al. (17) recommended flaxseed as the primary treatment for cyclical breast pain.

There was a significant reduction in mean VAS score from first visit to six months of flax seed intake. We also observed that there was a positive correlation between VAS score reduction from baseline to the first, third and six months of flax seed intake. Studies have shown the positive effects of phytoestrogens such as soy phytoestrogens (18, 19) in alleviating cyclical breast pain. Phytoestrogens have structural similarities to 17-estradiol and selectively influence estrogen receptors (20). Traditionally, flaxseed has been used to relieve cyclical breast pain and menopausal symptoms in humans and these authors proposed the hypothesis that the hormonal effects of flaxseed might improve symptoms of cyclical breast pain and tenderness.

Vaziri et al. (9) investigated the effects of flaxseed and omega-3 fatty acids on mastalgia. They demonstrated that flaxseed significantly reduced the mean score of cyclical breast pain compared to omega-3 fatty acids. In their study, 61, 60, and 60 women, respectively, were given flaxseed used to make bread, omega-3 fatty acids as pearls, and wheat bread as part of their diet for two menstrual cycles. Participants could consume the bread slices in one or three meals as preferred. Flaxseed and wheat bread were produced by the same companies, and the intervention method for wheat bread was identical to that of flaxseed. The results indicated that a flaxseed bread diet effectively reduced cyclical mastalgia and could be recommended to women as a straightforward treatment with minimal complications (9). Similarly, Godazandeh et al. (21) observed a significant reduction in VAS score (p<0.001) after using flaxseed oil to treat mastalgia from baseline to two months.

Flaxseed contains essential unsaturated fatty acids that stimulate the synthesis of omega-3 fatty acids. This process results in a decrease in the production of certain arachidonate metabolites, leading to the generation of eicosanoids with reduced pro-inflammatory effects. Eicosanoids derived from omega-3, which is present in flaxseed, demonstrate anti-inflammatory properties, contrasting with the inflammatory nature of omega-6 found in evening primrose. Furthermore, flaxseed is rich in lignan, an antioxidant that inhibits aromatase enzyme activity. This inhibition reduces estrogen production, thus playing a role in preventing estrogen-related cancers like breast cancer (22). The chemical structure of lignans is akin to estrogen receptor selective modulators like tamoxifen, a hormonal drug treatment for periodic breast pain (23).

Flaxseed is gaining recognition as a crucial functional food ingredient due to its abundant content of α-linolenic acid (ALA, an omega-3 fatty acid), lignans, and fiber. Flax protein contributes to the prevention and treatment of heart disease and supports immune system function, offering potential benefits for conditions such as osteoporosis, autoimmune disorders, and neurological conditions (24).

In the present study, flaxseed intake notably enhanced the quality of life for mastalgia patients across both physical and mental domains. Patients reported an overall health improvement, including alleviation of lower back pain, increased stamina, and reduced hair fall in many cases. In those patients who had dysmenorrhoea and irregular menstrual cycle also had improvement in their menstrual abnormalities. Prior studies had not investigated the impact of flaxseed on quality of life, though mastalgia's effect on quality of life had been examined. Kanat et al. (25) discovered that patients with mastalgia, assessed using the SF-36 questionnaire, had lower quality of life compared to a control group without mastalgia, with significant differences observed in physical function (p = 0.04), body pain (p = 0.02), general health (p = 0.03), and energy (p = 0.008). Another study compared quality of life between eastern and western populations in Turkey. Based on SF-36 results, the mean scores for physical function, physical role difficulty, and social function were significantly lower in the eastern group than in the western group (p = 0.029, p = 0.002, and p = 0.001, respectively). The mean scores in both groups were comparable to the baseline mean SF-36 scores in the present study (26). Although these studies didn't assess pre-post changes in SF-36 scores following intervention, they did highlight the lower quality of life scores among mastalgia patients.

The limitation of our study was that sample size was less which does not allow the generalisability of the results. Secondly, there was no control group to compare with. The results of the current study when compared with a control group would give a better insight towards the role of flaxseed in treating mastalgia. No scales were used to measure the patient's anxiety and depression, a limitation which should be addressed in further studies of the effect on qulaity of life with control groupsc to assess the effect of flaxseed intake in patients with mastalgia.

Evidence suggests that flax seed is beneficial in treating mastalgia and also has other benefits. The only drawback observed in our study participants was that, because of an intake of 30 g of roasted flax seed powder (approximately two tablespoons daily), it was difficult to swallow and prepare. Some participants also complained of increased stomach acidity due to flax seed powder intake. Other studies have used flaxseed in other forms, such as baked into bread to make it palatable. It was also observed that participants had a better digestion, lesser hair fall and reduced back ache after long term use of flax seed.

Ethics Committee Approval: Ethical approval for the study was obtained from the Dr. Ram Manohar Lohia Institute of Medical Sciences Ethical Committee (approval number: 96/22, date: 15.09.2022).

Informed Consent: Informed consent was obtained from all the participants.

Authorship Contributions: Surgical and Medical Practices: P.R., A.S., R.S.; Concept: P.R., A.S.; Design: P.R., A.S.; Data Collection and/or Processing: T.A., P.R.; Analysis and/or Interpretation: T.A., P.R.; Literature Search: R.S., S.S., V.R.G.; Writing: T.A..

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

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

References

1. Smith RL, Pruthi S, Fitzpatrick LA. Evaluation and management of breast pain. Mayo Clin Proc. 2004; 79: 353-372. (PMID: 15008609) [Crossref]
2. Stachs A, Stubert J, Reimer T, Hartmann S. Benign Breast Disease in Women. Dtsch Arztebl Int. 2019; 116: 565-574. (PMID: 31554551) [Crossref]
3. Singh A, Rai P, Mani R, Srivastava R, Singh S, Jauhari S, et al. Effect of reassurance and lifestyle modifications in treating Mastalgia:-Evidence from a Tertiary Care Centre of Northern India. International Journal of Surgery and Medicine. 2021; 7: 9-13. [Crossref]
4. Colak T, Ipek T, Kanik A, Ogetman Z, Aydin S. Efficacy of topical nonsteroidal antiinflammatory drugs in mastalgia treatment. J Am Coll Surg. 2003; 196: 525-530. (PMID: 12691925) [Crossref]
5. Pankaj H, Rai P, Singh A, Singh S, Srivastava R, Rudramani. Role of Reassurance and Proper Mechanical Support Advice on Quality of Life and Pain Relief in Patients of the Mastalgia-A Prospective Follow-up Study at A Tertiary Care Center in a Developing Country. Eur J Breast Health. 2023; 19: 210-214. (PMID: 37415657) [Crossref]
6. Pan A, Chen M, Chowdhury R, Wu JH, Sun Q, Campos H, et al. α-Linolenic acid and risk of cardiovascular disease: a systematic review and meta-analysis. Am J Clin Nutr. 2012; 96: 1262-1273. (PMID: 23076616) [Crossref]
7. Mohammadi-Sartang M, Mazloom Z, Raeisi-Dehkordi H, Barati-Boldaji R, Bellissimo N, Totosy de Zepetnek JO. The effect of flaxseed supplementation on body weight and body composition: a systematic review and meta-analysis of 45 randomized placebo-controlled trials. Obes Rev. 2017; 18: 1096-1107. (PMID: 28635182) [Crossref]
8. Goyal A, Sharma V, Upadhyay N, Gill S, Sihag M. Flax and flaxseed oil: an ancient medicine & modern functional food. J Food Sci Technol. 2014; 51: 1633-1653. (PMID: 25190822) [Crossref]
9. Vaziri F, Zamani Lari M, Samsami Dehaghani A, Salehi M, Sadeghpour H, Akbarzadeh M, et al. Comparing the Effects of Dietary Flaxseed and Omega-3 Fatty Acids Supplement on Cyclical Mastalgia in Iranian Women: A Randomized Clinical Trial. Int J Family Med. 2014; 2014: 174532. (PMID: 25197571) [Crossref]
10. Bonacchi A, Chiesi F, Lau C, Marunic G, Saklofske DH, Marra F, et al. Rapid and sound assessment of well-being within a multi-dimensional approach: The Well-being Numerical Rating Scales (WB-NRSs). PloS One. 2021; 16: e0252709. (PMID: 34125831) [Crossref]
11. Fakhravar S, Bahrami N, Qurbani M, Olfati F. The Effect of Healthy Lifestyle Promotion Intervention on Quality of Life in Cyclic Mastalgia via Individual Counseling: A Randomized Controlled Clinical Trial. Int J Community Based Nurs Midwifery. 2021; 9: 55-63. (PMID: 33521149) [Crossref]
12. Mohammed AA. Evaluation of mastalgia in patients presented to the breast clinic in Duhok city, Iraq: Cross sectional study. Ann Med Surg (Lond). 2020; 52: 31-35. (PMID: 32194960) [Crossref]
13. Sunil Krishna M, Shenoy RK. Clinical profile of cyclical and noncyclical Mastalgia. New Indian Journal of Surgery. 2018; 9: 764-770. [Crossref]
14. Albertazzi P, Purdie DW. Reprint of The nature and utility of the phytoestrogens: a review of the evidence. Maturitas. 2008; 61: 214-226. (PMID: 19434893) [Crossref]
15. Bryant M, Cassidy A, Hill C, Powell J, Talbot D, Dye L. Effect of consumption of soy isoflavones on behavioural, somatic and affective symptoms in women with premenstrual syndrome. Br J Nutr. 2005; 93: 731-739. (PMID: 15975174) [Crossref]
16. Goss PE, Li T, Theriault M, Pinto S, Thompson L. Effects of dietary flaxseed in women with cyclical mastalgia. Breast Cancer Research and Treatment. 2000; 64: 153. [Crossref]
17. Rosolowich V, Saettler E, Szuck B, Lea RH, Levesque P, Weisberg F, et al. RETIRED: Mastalgia. J Obstet Gynaecol Can. 2006; 28: 49-57. (PMID: 16533457) [Crossref]
18. McFadyen IJ, Chetty U, Setchell KD, Zimmer-Nechemias L, Stanley E, Miller WR. A randomized double blind-cross over trial of soya protein for the treatment of cyclical breast pain. Breast. 2000; 9: 271-276. (PMID: 14732177) [Crossref]
19. Ingram DM, Hickling C, West L, Mahe LJ, Dunbar PM. A double-blind randomized controlled trial of isoflavones in the treatment of cyclical mastalgia. Breast. 2002; 11: 170-174. (PMID: 14965665) [Crossref]
20. Mirghafourvand M, Mohammad Alizadeh Charandabi S, Javadzadeh Y, Ahmadpour P. Comparing the effects of vitexagnus and flaxseed on premenstrual symptoms: a randomized controlled trial. Journal of Hayat. 2015; 21: 68-78. [Crossref]
21. Godazandeh G, Ala S, Motlaq TM, Sahebnasagh A, Bazi A. The comparison of the effect of flaxseed oil and vitamin E on mastalgia and nodularity of breast fibrocystic: a randomized double-blind clinical trial. J Pharm Health Care Sci. 2021; 6: 4. (PMID: 33407941) [Crossref]
22. Jaafarnejad F, Hosseini SF, Mazlom SR, Hami M. Comparison of the effect of fish oil and vitamin E on the duration of Cyclic mastalgia. Evidence Based Care. 2013; 3: 69-76. [Crossref]
23. Thompson LU, Chen JM, Li T, Strasser-Weippl K, Goss PE. Dietary flaxseed alters tumor biological markers in postmenopausal breast cancer. Clin Cancer Res. 2005; 11: 3828-3835. (PMID: 15897583) [Crossref]
24. Noreen S, Tufail T, Ul Ain HB, Awuchi CG. Pharmacological, nutraceutical, and nutritional properties of flaxseed (Linum usitatissimum): An insight into its functionality and disease mitigation. Food Sci Nutr. 2023; 11: 6820-6829. (PMID: 37970400) [Crossref]
25. Kanat BH, Atmaca M, Girgin M, Ilhan YS, Bozdağ A, Özkan Z, et al. Effects of Mastalgia in Young Women on Quality of Life, Depression, and Anxiety Levels. Indian J Surg. 2016; 78: 96-99. (PMID: 27303116) [Crossref]
26. Oner G, Bahce ZS, Yıldırım NK, Yanar F, Silahsızoğlu B, Haslak A, et al. Psychological Symptoms and Health Related Quality of Life in Patients with Mastalgia: Sociocultural differences in patient with mastalgia. Archives of Breast Cancer 2022; 9: 474-479. [Crossref]

Case Report

Eur J Breast Health 2024; 20(4): 309-312
DOI: 10.4274/ejbh.galenos.2024.2024-5-10

Rare Breast Emergency: A Case of Necrotizing Fasciitis of the Breast in a Lactating Patient

Gökhan Giray Akgül[1], Sümeyra Güler[1], Simay Akyüz[2], Duygu Bayram[3], İbrahim Burak Bahçecioğlu[1], Müjdat Turan[2], Hikmet Erhan Güven[2], Mehmet Ali Gülçelik[1], Kerim Bora Yılmaz[2]

[1]Department of Surgical Oncology, Gülhane Training and Research Hospital, University of Health Sciences Turkey, Ankara, Turkey
[2]Department of General Surgery, Gülhane Training and Research Hospital, University of Health Sciences Turkey, Ankara, Turkey
[3]Department of Pathology, Gülhane Training and Research Hospital, University of Health Sciences Turkey, Ankara, Turkey

ABSTRACT

Necrotizing fasciitis is a rare but potentially lethal infection of the skin and soft tissue, commonly seen in the perianal and gluteal regions. Concomitant diabetes is a predisposing factor. Primary necrotizing fasciitis of the breast is rare in healthy women. In this article, we present a very rare case of breast necrotizing fasciitis in the context of the literature. We report the case of a 35-year-old female patient who had given birth two months prior to admission and developed necrotizing fasciitis of the breast during lactation. The patient presented to the emergency department with sepsis. Examination revealed widespread erythema, dark discoloration, edema, and necrotic areas indicative of wet gangrene and crepitation in the left breast. Necrotizing fasciitis is a rapid and aggressive disease that can be fatal, and delayed diagnosis may unfortunately result in death. Therefore, careful evaluation of all suspected cases, especially for patients with risk factors, is crucial for early diagnosis and timely treatment. This case highlights the importance of recognizing necrotizing fasciitis of the breast in lactating women to ensure prompt and appropriate management, potentially saving lives.

Keywords: Necrotising fasciitis; lactation; bioactive wound dressings; negative pressure wound therapy; split thickness skin graft

Cite this article as: Akgül GG, Güler S, Akyüz S, Bayram D, Bahçecioğlu İB, Turan M, Güven HE, Gülçelik MA, Yılmaz KB. Rare Breast Emergency: A Case of Necrotizing Fasciitis of the Breast in a Lactating Patient. Eur J Breast Health. 2024; 20(4): 309-312

Key Points

- Primary necrotizing fasciitis of the breast is extremely rare in healthy women.
- The progressive infection developing due to trauma during lactation can lead to significant mortality and morbidity if diagnosed late. This underscores the need for clinicians to consider progressive infections in lactating patients in the differential diagnosis, even in the absence of common predisposing factors such as diabetes.
- The patient's breast was preserved through emergency surgical debridement, negative pressure wound therapy, and bioactive wound dressings.

Introduction

Necrotizing fasciitis (NF) is an aggressive, necrotic, and life-threatening infection of the soft tissues. It is progressive by nature and is accompanied by arterial thrombosis, leading to gangrene of the skin and subcutaneous tissues, as well as manifestations of severe sepsis, multiple organ failure, and death (1). The progressive nature of the disease is characterized by an increase in pressure caused by the infection in the closed fascial plane and its ability to spread towards low-pressure areas along the fascial plane and affect surrounding tissues in other areas (2, 3). Disease progression and local regional damage are determined by compartment syndrome and ischemic necrosis at the capillary level due to increased pressure.

Treatment of these infections is primarily surgical, and debridement, abscess drainage, and pressure reduction are necessary to prevent disease progression. Septic shock and its associated complications are linked to mortality rates of almost 90% following treatment delays (4). Primary necrotizing fasciitis of the breast (PNFB) is extremely rare and NF is most commonly observed in the extremities, perineum, and abdominal wall. In recent years, PNFB cases have been presented in the literature more often, and this increase may be related to the rising incidence of diabetes mellitus, which is considered an important comorbidity of NF (5).

In this study, we report a case of NF in a lactating patient which was thought to have developed as a result of trauma due to breastfeeding.

Corresponding Author:
Kerim Bora Yılmaz; kerimbora.yilmaz@sbu.edu.tr

Received: 29.05.2024
Accepted: 15.06.2024
Available Online Date: 26.09.2024

The patient underwent a breast-conserving procedures and skin graft reconstruction.

Case Presentation

A 35-year-old female patient presented to the emergency department two months after giving birth to her third child. She had a nipple fissure caused by breastfeeding trauma and was unable to breastfeed for three days. One week before admission, she experienced pain, swelling, and increased breast temperature. She had a history of irregular and short-term amoxicillin and clavulanic acid use.

In the left breast, there was widespread erythema, dark color changes, edema, and necrotic areas, consistent with wet gangrene, as well as crepitation (Figure 1).

Hospitalization was recommended for this patient with a pre-diagnosis of sepsis and elevated acute-phase reactants levels [C-reactive protein (CRP) 305 mg/dL; white blood cell (WBC) count 20.4×10^3 cells/µL; hemoglobin A1c 5.2%]. Urgent debridement was planned during hospitalization, but the patient refused treatment. On the night of the same day, the patient was re-admitted to the emergency department because of the progression of her complaints. Based on physical examination findings, the patient was admitted to the general surgery department. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was 8 at the time of hospitalization (6). With the diagnosis of NF, necrotic areas up to a depth of approximately 3 cm from the subcutaneous tissue were debrided under emergency conditions, and negative pressure wound therapy (NPWT) was applied using Genadyne Silver Foam® for infection and exudate control in the wound area. The patient underwent repeated debridement and breast-conserving surgery followed by NPWT. The patient was spared from mastectomy through effective surgical debridements with clear surgical margins and the application of NPWT (Figure 2). Empirical antibiotic therapy was initiated with piperacillin tazobactam (4×4.5 mg) and teicoplanin (1×400 mg). *Streptococcus pyogenes* (group A *Streptococcus*, teicoplanin-sensitive) was detected in the tissue culture. Cabergoline (Dostinex 0.5®) was administered in tablet form (0.5 mg) based on the recommendation of the endocrinology department to stop lactation, which impairs wound healing. Hyperbaric treatment, which was deemed appropriate, could not be administered because of patient refusal. The patient, whose infection findings regressed with repeated debridements and who developed healthy granulation tissue, was planned for reconstruction with a graft (Figure 3). During outpatient follow-up, the patient received intermittent NPWT and bioactive wound dressings were applied. A collagen/laminin-based dermal matrix containing resveratrol-loaded microparticles was used to fill the tissue defects and promote further granulation (Figure 3). During outpatient follow-up, granulation in the tissue defect reached the skin level, and reconstruction via grafting was performed (Figure 3). Figure 4 (A) and (B) show pathological specimens obtained from the patient, with one sample showing severe inflammation and a duct rich in neutrophils that had broken down the breast lobules. Written informed consent was obtained from the patient.

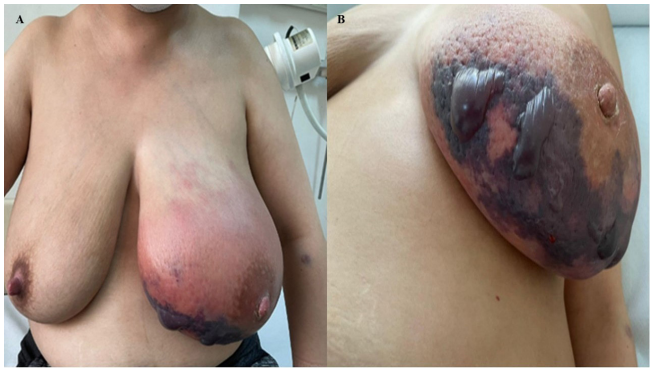

Figure 1. A, B. There was widespread erythema, dark colour changes, oedema, and necrotic areas consistent with wet gangrene

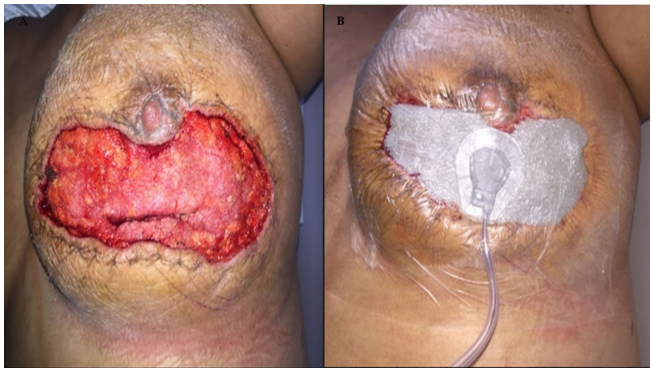

Figure 2. A, B. Application of negative pressure wound therapy after debridement

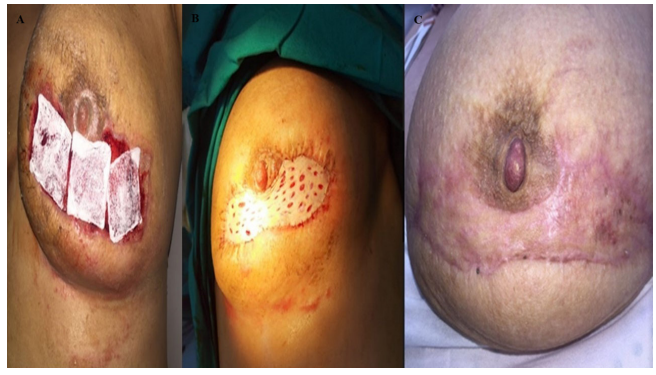

Figure 3. A. Increasing granulation with bioactive dressings; **B.** Reconstruction with a graft after the infection was brought under control; **C.** Epitelization

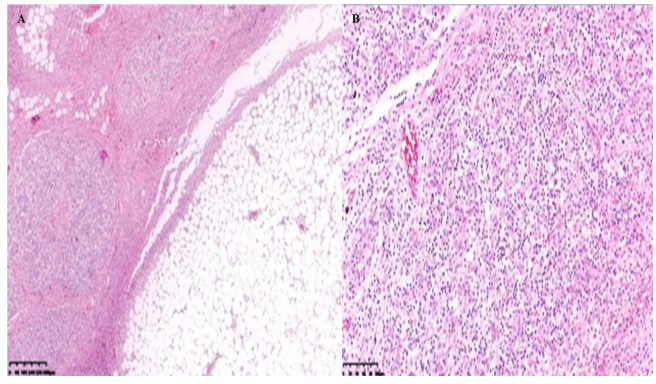

Figure 4. A. Severe inflammation that advanced into the adipose tissue disrupted the breast lobules (haematoxylin and eosin, magnification of 4×); **B.** Severe inflammation rich in neutrophils. Destruction of the duct is seen in the middle (haematoxylin and eosin, magnification of 10×)

Discussion and Conclusion

Although rare, NF is extremely aggressive. The course of the disease is characterized by different symptoms according to the area of disease involvement in the skin and subcutaneous and fascial tissues. Breast involvement is very rare, but can complicate the differential diagnosis of the disease. PNFB is often misdiagnosed and mistakenly confused with other breast diseases, such as cellulitis, mastitis, abscess, or inflammatory breast cancer (7, 8). The mortality rates reported in the literature are generally related to delayed diagnosis and treatment, as was the case for two patients in our previous series of five patients (2). However, the development of this disease remains unclear. Late diagnosis and inadequate treatment of primary breast infections may result in cellulitis, breast abscess, or the progression of an infectious disease to PNFB. If the infection in our lactating patient had been treated with an appropriate surgical method and antibiotic therapy, we might not have encountered a progressive infection. A history of fissures due to breastfeeding in our patient was associated with trauma. Post-traumatic NF of the breast tissue has been reported in the literature, but it has been described most frequently after surgical interventions (7, 9).

Advanced age, diabetes mellitus, chronic alcoholism, obesity, immunosuppression, vascular disease, malignancy, skin biopsies, and trauma are risk factors for the development of NF (2, 7, 8). Our patient was not diabetic, but was lactating, and she was referred to our hospital for a breast infection. Broad-spectrum antibiotics are preferred for the initial administration of empirical antibiotics. Definitive antibiotic therapy should be administered based on the microbial results obtained from tissue cultures after intraoperative debridement. It must be noted that the disease has a progressive nature and is a clinical entity that can be controlled surgically.

Our patient was diagnosed with type II monomicrobial infection secondary to group A beta-hemolytic *Streptococcus* (9). In such cases, treatment approaches include appropriate fluid and electrolyte administration under emergency and intensive care unit conditions, broad-spectrum antibiotic therapy until culture results are available, and timely application of aggressive surgical debridement. Very high mortality rates have been reported in cases of delayed treatment, especially in patients with comorbidities, which are related to the diagnosis time. The extent of surgery was determined based on the principle of not leaving any necrotic tissue. The circummammary ligament anchors the superficial fascia of the breast to the deep fascia of the chest at the perimeter. Cooper ligaments, which are specialized vertical cutaneous ligaments that anchor the skin, travel from the posterior lamina fascia through the breast gland to the anterior lamina. When planning treatment, these anatomical structures and fascial connections should be considered as they may influence the progression and spread of NF (10). To date, various operations have been performed in such cases, ranging from selective debridement to radical mastectomy, as reported in the literature. This wide range of treatments is due to differences in the spread of necrotic tissue and efforts to control the spread of infection. In the clinical stage at which treatment was initiated for the patient presented here, a response to infection was achieved with extensive surgical debridement, allowing the patient to be spared from radical mastectomy. NPWT is routinely used in these dressings, especially after surgical debridement of the infected tissues. NPWT products with instillation or products containing silver sponges are generally preferred after the first debridement. When the infection is brought under control, closure of the defect becomes a priority (11, 12). NPWT creates tension, which stimulates the production of granulation tissue and reduces wound size and bacterial load by contracting the wound (13). Upon increasing the microcirculatory blood supply with NPWT, inflammatory cells migrate to the wound region, resulting in the elimination of extravascular edema (14). Compared with traditional dressings, this approach also promotes and accelerates the formation of granulation tissue by removing bacteria, end products, exudates, and debris. Furthermore, it stimulates angiogenesis and secures wound coverage, thereby facilitating wound healing (15).

Detailed physical examination is required to diagnose NF in patients with basic skin changes. Laboratory tests and imaging studies may be necessary in cases with suspicious skin findings. Wong et al. (6) developed the LRINEC scoring system. Based on serum CRP, WBC count, hemoglobin, sodium, creatinine, and glucose values, the present case scored 8 points, putting the patient in the high-risk category at the time of diagnosis. Values of ≥8 increase the risk of NF development by 75% (16). Additionally, based on clinical findings, the case was classified as grade 3 (late stage) due to crepitation, darkening of the skin, and tissue necrosis reaching the gangrene level (17). Since the patient had an advanced clinical stage and a high LRINEC score, diagnostic imaging was not considered necessary, and it was not performed to avoid treatment delays and disease progression. The progressive nature of the disease, septic status, and related risks should be considered, and surgical consent for mastectomy and chest wall debridement should be obtained. Debridement of the surrounding tissues should also be performed as necessary when the disease spreads to the skin of the arm or abdomen (2, 18). Large tissue defects may occur after debridement, and interventions for vascular and neural structures may be required, especially in cases extending to the axillary region where vascular and neural structures are involved. If NPWT is applied in this region, barrier protectors for vascular and neural structures should be used (2).

Tissue-engineered biomaterials that play an active role in wound healing are called bioactive wound dressings. These materials, which contain natural extracellular matrix components and provide structural support for tissue repair owing to their biocompatible structures, contain polymers, such as collagen, hyaluronic acid, chitosan, and alginate.

In our patient, treatment with dipalmitoylphosphatidylcholine (DPPC)-based microparticles added to a 3- dimensional porous collagen laminin matrix was used to fill the tissue defect with granulation and prepare the wound bed for grafting after infection was controlled (19). The presence of the glycosaminoglycan derivative hyaluronic acid, collagen/hydrophilic properties, gelatine providing a 3-dimensional pore structure, laminin as a cell-binding protein, DPPC in the cell membrane, and resveratrol as an antioxidant in this wound dressing enabled the preparation of the wound bed after the infection was controlled and before grafting (20). Split-thickness skin grafting prevents the loss of protein by covering the granulated tissues and enables closure of the area in question to avoid infection and facilitate rapid epithelisation (21).

Although rarely reported in the literature, breast NF is an often-deadly disease that spreads rapidly and aggressively. Several confounding factors may have resulted in delayed diagnosis and mortality. For early diagnosis and timely treatment, it is essential that all suspected cases be evaluated carefully and thoroughly, regardless of the patient's

age. This is particularly important for patients with risk factors and comorbidities.

Informed Consent: Written informed consent was obtained from the patient.

Authorship Contributions

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

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. Singh A, Ahmed K, Aydin A, Khan MS, Dasgupta P. Fournier's gangrene. A clinical review. Arch Ital Urol Androl. 2016; 88: 157-164. (PMID: 27711086) [Crossref]
2. Yilmaz KB, Saydam M, Akinci M, Akkoca M, Arikok AT, Guler S, et al. Primary necrotizing fasciitis of the breast. Case series with 5 patients. J Infect Dev Ctries. 2022; 16: 902-908. (PMID: 35656964) [Crossref]
3. Kim J, Yoo G, Lee T, Kim JH, Seo DM, Kim J. Classification Model for Diabetic Foot, Necrotizing Fasciitis, and Osteomyelitis. Biology (Basel). 2022; 11: 1310. (PMID: 36138789) [Crossref]
4. Chernyadyev SA, Ufimtseva MA, Vishnevskaya IF, Bochkarev YM, Ushakov AA, Beresneva TA, et al. Fournier's Gangrene: Literature Review and Clinical Cases. Urol Int. 2018; 101: 91-97. (PMID: 29949811) [Crossref]
5. Misiakos EP, Bagias G, Patapis P, Sotiropoulos D, Kanavidis P, Machairas A. Current concepts in the management of necrotizing fasciitis. Front Surg. 2014; 1: 36. (PMID: 25593960) [Crossref]
6. Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med. 2004; 32: 1535-1541. (PMID: 15241098) [Crossref]
7. Cai Y, Cai Y, Shi W, Feng Q, Zhu L. Necrotizing Fasciitis of the Breast: A Review of the Literature. Surg Infect (Larchmt). 2021; 22: 363-373. (PMID: 33026953) [Crossref]
8. Konik RD, Huang GS. Management of Primary Necrotizing Fasciitis of the Breast: A Systematic Review. Plast Surg (Oakv). 2020; 28: 215-221. (PMID: 33215036) [Crossref]
9. Gupta A Dr, Gupta A, Ravi B Dr, Mundra M Dr, Sandhu H Dr, Agrawal S Dr, et al. Post-traumatic necrotising fasciitis of the breast: a case study with literature review. J Wound Care. 2019; 28: 775-778. (PMID: 31721667) [Crossref]
10. Rehnke RD, Groening RM, Van Buskirk ER, Clarke JM. Anatomy of the Superficial Fascia System of the Breast: A Comprehensive Theory of Breast Fascial Anatomy. Plast Reconstr Surg. 2018; 142: 1135-1144. (PMID: 30511967) [Crossref]
11. Khansa I, Schoenbrunner AR, Kraft CT, Janis JE. Silver in Wound Care-Friend or Foe?: A Comprehensive Review. Plast Reconstr Surg Glob Open. 2019; 7: e2390. (PMID: 31592393) [Crossref]
12. Bukovcan P, Koller J, Hajská M, Záhorec P. Clinical Experience With the Use of Negative Pressure Wound Therapy Combined With a Silver-impregnated Dressing in Mixed Wounds: A Retrospective Study of 50 Cases. Wounds. 2016; 28: 255-263. (PMID: 27560468) [Crossref]
13. Hu J, Goekjian S, Stone N, Nelson A, Cooper MJ. Negative Pressure Wound Therapy for a Giant Wound Secondary to Malignancy-induced Necrotizing Fasciitis: Case Report and Review of the Literature. Wounds. 2017; 29: E55-E60. (PMID: 28862979) [Crossref]
14. Apelqvist J, Willy C, Fagerdahl AM, Fraccalvieri M, Malmsjö M, Piaggesi A, et al. EWMA Document: Negative Pressure Wound Therapy. J Wound Care. 2017; 26: S1-S154. (PMID: 28345371) [Crossref]
15. Normandin S, Safran T, Winocour S, Chu CK, Vorstenbosch J, Murphy AM, et al. Negative Pressure Wound Therapy: Mechanism of Action and Clinical Applications. Semin Plast Surg. 2021; 35: 164-170. (PMID: 34526864) [Crossref]
16. Bechar J, Sepehripour S, Hardwicke J, Filobbos G. Laboratory risk indicator for necrotising fasciitis (LRINEC) score for the assessment of early necrotising fasciitis: a systematic review of the literature. Ann R Coll Surg Engl. 2017; 99: 341-346. (PMID: 28462647) [Crossref]
17. Chaomuang N, Khamnuan P, Chuayunan N, Duangjai A, Saokaew S, Phisalprapa P. Novel Clinical Risk Scoring Model for Predicting Amputation in Patients With Necrotizing Fasciitis: The ANF Risk Scoring System. Front Med (Lausanne). 2021; 8: 719830. (PMID: 34869417) [Crossref]
18. Ucar EA, Durur-Subasi I, Yilmaz KB, Arikok AT, Hekimoglu B. Quantitative perfusion parameters of benign inflammatory breast pathologies: A descriptive study. Clin Imaging. 2020; 68: 249-256. (PMID: 32911313) [Crossref]
19. Eroğlu İ, Gökçe EH, Tsapis N, Tanrıverdi ST, Gökçe G, Fattal E, et al. Evaluation of characteristics and in vitro antioxidant properties of RSV loaded hyaluronic acid-DPPC microparticles as a wound healing system. Colloids Surf B Biointerfaces. 2015; 126: 50-57. (PMID: 25543983) [Crossref]
20. Gokce EH, Tuncay Tanrıverdi S, Eroglu I, Tsapis N, Gokce G, Tekmen I, et al. Wound healing effects of collagen-laminin dermal matrix impregnated with resveratrol loaded hyaluronic acid-DPPC microparticles in diabetic rats. Eur J Pharm Biopharm. 2017; 119: 17-27. (PMID: 28461085) [Crossref]
21. Saydam M, Yılmaz KB, Bostancı MT, Turan M, Akıncı M, Yılmaz İ, et al. The use of autologous epidermal grafts for diabetic foot ulcer emergencies: A clinical study. Ulus Travma Acil Cerrahi Derg. 2022; 28: 262-267. (PMID: 35485568) [Crossref]

Case Report

Eur J Breast Health 2024; 20(4): 313-315
DOI: 10.4274/ejbh.galenos.2024.2024-4-5

Pseudoaneurysm in the Axillary Tail of the Breast After A Core Needle Biopsy

Cedric Pluguez-Turull[1], Cinthia Del Toro[2], Nicole Brofman[1], Yara Z. Feliciano[1]

[1]Department of Radiology, University of Miami Miller School of Medicine, Sylvester Cancer Center, and Jackson Memorial Hospital, Florida, USA
[2]University of Miami, Leonard M. Miller School of Medicine, Florida, USA

ABSTRACT

We present the case of a forty-year-old asymptomatic female with no personal or family history of breast cancer, who underwent a core needle biopsy (CNB) following the identification of a focal asymmetry in the right breast on screening mammography. Eight months later, a prominent adjacent vascular structure with a round outpouching was detected on breast ultrasound, confirmed as a post-biopsy pseudoaneurysm. Breast pseudoaneurysms, although exceedingly rare, result from inadvertent vessel puncture during core needle biopsies, particularly when larger gauge needles are used. They present as palpable, throbbing lumps in the breast and are well-defined heterogeneous structures that exhibit turbulent flow with a feeding artery on color Doppler imaging. This swirling sign showing a to-and-fro waveform is also known as the "yin-yang" sign on Doppler ultrasound. Post-CNB pseudoaneurysms in the breast, while rare, should be considered as potential complications following core need biopsy. Understanding their characteristic imaging features, risk factors, and available management options is essential for early diagnosis and appropriate treatment. This case underscores the importance of vigilance in biopsy procedures and the need for prompt recognition and intervention in case of such complications.

Keywords: Ultrasound-guided core needle biopsy; vascular mass; pseudoaneurysm; yin-yang sign; CT angiogram; arterial phase hyperenhancement; thrombin

Cite this article as: Pluguez-Turull C, Toro CD, Brofman N, Feliciano YZ. Pseudoaneurysm in the Axillary Tail of the Breast After A Core Needle Biopsy. Eur J Breast Health. 2024; 20(4): 313-315

Key Points

- Although rare, breast pseudoaneurysms can occur as complications following core needle biopsies, especially when using larger gauge needles. Clinicians should be aware of this possibility and consider it in the differential diagnosis of palpable lumps or unusual vascular structures detected during follow-up imaging.
- Understanding the characteristic imaging features of breast pseudoaneurysms is crucial for accurate diagnosis. These features include well-defined heterogeneous structures with turbulent flow, often exhibiting the "yin-yang" sign on Doppler ultrasound.
- Management of breast pseudoaneurysms typically involves a multidisciplinary approach.

Introduction

Core needle biopsy (CNB) is a commonly performed procedure referred to as the gold standard for sampling suspicious lesions to obtain an accurate diagnosis (1). Given that CNB is both less invasive and less costly while maintaining accuracy in establishing a pathological diagnosis for suspicious breast lesions, it has the potential to effectively replace excisional biopsy (2). Complications following CNB of the breast are generally rare, occurring in less than 1% of cases. Some reported minor complications following CNB's of the breast include bruising, pain, and vasovagal reactions. More severe complications include severe bleeding, infection requiring antibiotics, and hematomas requiring treatment all occurring in less than 1% of cases (3).

Case Report and Discussion

A forty-year-old asymptomatic female with no personal or family history of breast cancer was sent for additional breast imaging after screening mammography identified a focal asymmetry in the right breast. Findings of a breast ultrasound included an indeterminate oval circumscribed hypoechoic solid mass in the right breast axillary tail region with an adjacent vessel (Figure 1). An ultrasound-guided CNB was recommended and performed with a 14-gauge needle. A biopsy marker was placed at the biopsy site and no complications occurred (Figure 2). The biopsy yielded benign lymphoid tissue.

Eight months later, the axillary mass appeared similar in appearance but a prominent adjacent vascular structure with a round outpouching was detected on breast ultrasound. It demonstrated classic "yin-yang" flow on color Doppler imaging consistent with a post-biopsy pseudoaneurysm (Figure 3).

Corresponding Author:
Cedric Pluguez-Turull; cxp932@med.miami.edu

Received: 07.05.2024
Accepted: 12.07.2024
Available Online Date: 26.09.2024

A breast pseudoaneurysm is a full thickness interruption of an arterial wall that typically results from an iatrogenic process (4). Breast pseudoaneurysms are very rare following CNBs and result from the accidental puncture of a vessel causing blood to leak into surrounding tissue. The latest The Breast Imaging Reporting and Data System lexicon categorizes pseudoaneurysms as a special case of vascular abnormality within its ultrasound section (5). The use of larger gauge needles increases the risk of a post-biopsy breast pseudoaneurysm typically presenting as a hematoma or palpable lump at the biopsy site.

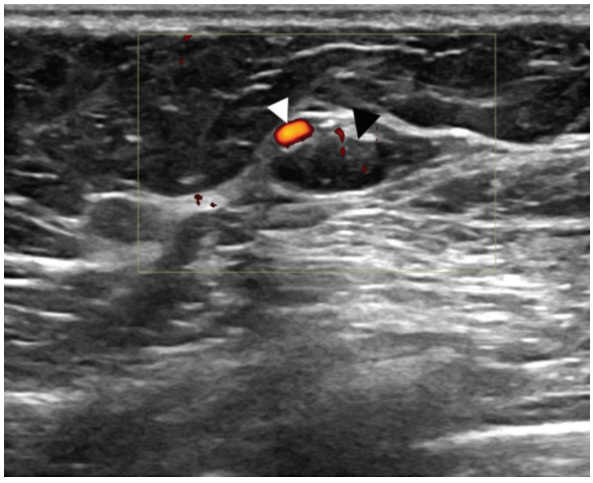

Figure 1. Baseline imaging showed an oval, parallel, circumscribed hypoechoic mass (black arrowhead) in the right axillary tail with evidence of internal vascular flow and peripheral flow versus vessel (white arrowhead) on power Doppler US imaging

US: Ultrasonography

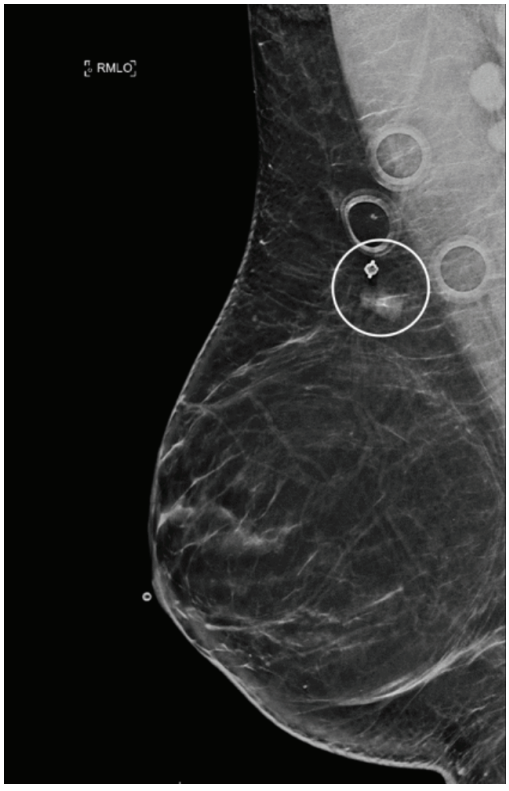

Figure 2. Right MLO mammogram demonstrates a postbiopsy clip placement in the right lower axillary tail (white circle)

MLO: The mediolateral oblique

Pseudoaneurysms are classically documented on ultrasound as a well-defined heterogenous structure that exhibits turbulent flow with a feeding artery on color Doppler imaging. This swirling sign showing a to-and-fro waveform is also known as the "yin-yang" sign (6). Computed tomography angiography can show pooled contrast within a breast mass focally dilated vascular structure in the region of the biopsy (4).

Computed tomography angiogram of the chest with intravenous contrast noted an approximately 0.4 x 0.6 cm soft tissue attenuation structure with evidence of mild contrast enhancement immediately adjacent to a small vessel in the lateral aspect of the right breast which could represent a small pseudoaneurysm, possibly with partial thrombosis (Figure 4).

Patients with a pseudoaneurysm following a CNB present with a palpable, and throbbing lump at the site of the biopsy in the breast (4). Some risk factors for developing a pseudoaneurysm include atherosclerosis, hypertension, anticoagulant therapy use, female sex, and older age (1).

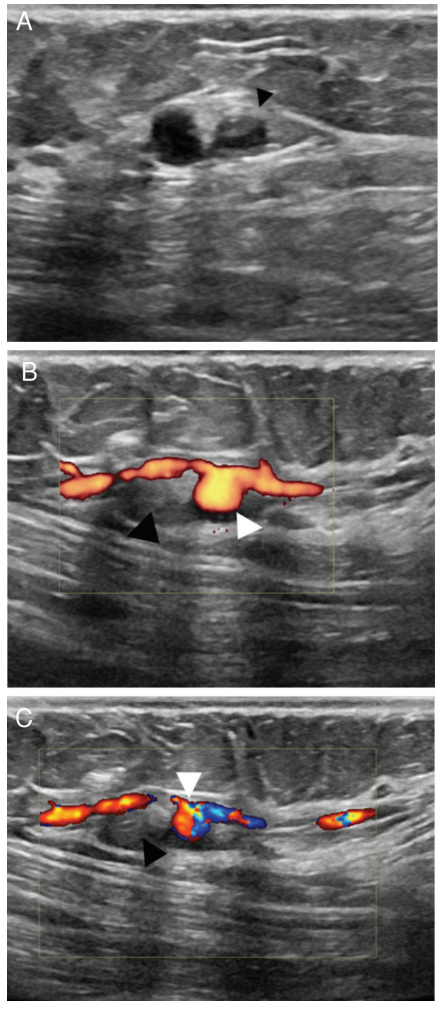

Figure 3. Grayscale ultrasound images **A.** In the right axillary tail reveal post-biopsy changes in the oval hypoechoic right axillary tail mass (black arrowhead). Follow-up ultrasound color Doppler images **B.** and **C.** In the right axillary tail demonstrate interval rounded outpouching of a vessel (white arrowhead) within the previously biopsied hypoechoic mass (black arrowhead). The outpouching demonstrates a characteristic internal "yin-yang" sign on color Doppler

The interventional radiology service was consulted, and the decision was made to deliver percutaneous thrombin injection directly into the pseudoaneurysm. The first line of treatment uses the ultrasound for manual compression. Delivery of percutaneous thrombin injections directly into the pseudoaneurysm or placement of an intravascular coil can also be done (4). Surgical access may be performed to ligate the affected vessel or excise the mass as well (6). However, considering that breast pseudoaneurysms don't result in significant morbidity or mortality, a conservative approach has also been proposed in the management of low-risk patients (1).

Subsequent follow-up with breast ultrasound demonstrated an interval decrease in size of the right axillary tail pseudoaneurysm along with stable status of the axillary mass which was previously biopsied (Figure 5).

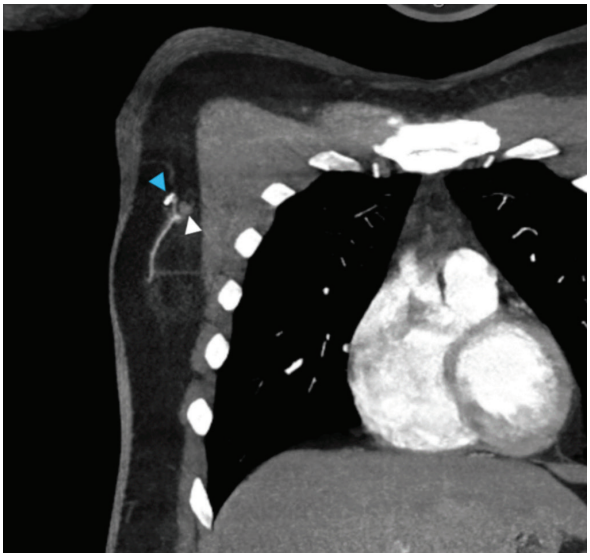

Figure 4. CT chest angiogram in arterial phase of contrast bolus and coronal MIP reconstruction demonstrates a saccular outpouching from a right axillary arterial vessel (white arrowhead) and adjacent hyperdense body, likely corresponding to post biopsy clip (blue arrowhead) at the site of previous biopsy

CT: Computed tomography; MIP: Maximum intensity projection

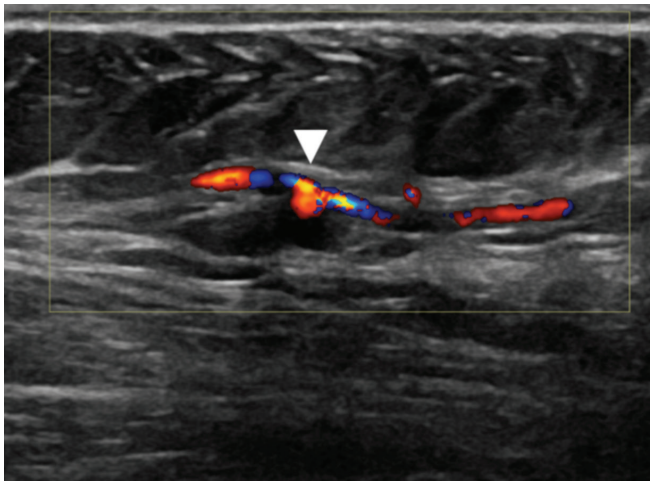

Figure 5. Additional follow-up with right axillary tail ultrasound with color Doppler technique demonstrates interval decreased size of the vascular outpouching (white arrowhead) after direct thrombin injection 5 months ago

Informed Consent: This manuscript does not involve experimental research on humans. This adult patient was consented for medical treatment and consented to the use of their non-identifiable medical data and photographs for educational purposes.

Authorship Contributions

Surgical and Medical Practices: C.P-T., Y.Z.F.; Concept: C.P-T., C.D.T., Y.Z.F.; Design: C.P-T., C.D.T.; Data Collection and/or Processing: C.P-T., C.D.T., N.B., Y.Z.F.; Analysis or Interpretation: C.P-T., C.D.T.; Literature Search: C.P-T., C.D.T., N.B., Y.Z.F.; Writing: C.P-T., C.D.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. Russell T, Creagh-Barry M. Breast pseudoaneurysm arising from core needle biopsy should be left well alone. BMJ Case Rep. 2017; 2017: bcr2017221546. Published 2017 Sep 28. [Crossref]
2. Davidson T, Ravid MM, Nissan E, Sklair-Levy M, Nissan J, Chikman B. Correlations Between Core Needle Biopsy and Excisional Biopsy Findings in Suspected Breast Lesions: A Single Center Study. Isr Med Assoc J. 2018; 20: 401-404. (PMID: 30109786) [Crossref]
3. Bruening W, Fontanarosa J, Tipton K, Treadwell JR, Launders J, Schoelles K. Systematic review: comparative effectiveness of core-needle and open surgical biopsy to diagnose breast lesions. Ann Intern Med. 2010; 152: 238-246. (PMID: 20008742) [Crossref]
4. Lee MV, Aripoli A, Messinger J. Pseudoaneurysm of the breast following stereotactic core needle biopsy. Breast J. 2019; 25: 1004-1005. (PMID: 31187513) [Crossref]
5. Spak DA, Plaxco JS, Santiago L, Dryden MJ, Dogan BE. BI-RADS® fifth edition: A summary of changes. Diagn Interv Imaging. 2017; 98: 179-190. (PMID: 28131457) [Crossref]
6. Farrokh D, Fallah-Rastegar Y, Abbasi B. Pseudoaneurysm of the breast after core needle biopsy: Successful treatment with focused ultrasound-guided compression. Breast J. 2019; 25: 312-313. (PMID: 30790385) [Crossref]

2024 Reviewer Index

Adnan Aydıner
Ajay Kumar
Alexander Mundinger
Ali Zaid Al-Saffar
Alper Öztürk
Atilla Soran
Ayfer Kamalı Polat
Ayşe Nilüfer Özaydın
Ayşegül Akdoğan Gemici
Banu Arun
Bartu Badak
Bekir Kuru
Beyza Özçınar
Bülent Koca
Çağlar Ünal
Çetin Ordu
Cihangir Özaslan
Daniel Rodrigues de Bastos
Didier Verhoeven
Dlnya Asad Mohamad
Efe Sezgin
Eli Avisar
Enver Özkurt
Erkin Aribal
Esma Özmen
Fatih Aydoğan
Fatma Aktepe
Federica Martorana
Fikriye Figen Ayhan
Filiz Çelebi
Filiz İzci
Filiz Salman Saraç
Funda Dinç
Görkem Aksu
Gül Esen İçten
Güldeniz Karadeniz Çakmak
Gürsel Soybir
Hasan Karanlık
Hüseyin Özgür Aytaç
Ismail Jatoi
Jeffrey Falk
Kanay Yararbas
Kandace McGuire
Levent Yeniay
Mauricio MagalhaesCosta
Mehmet Ali Nazlı
Melis Gültekin
Mireille Van Goethem
Mürsel Düzova
Mustafa Emiroroğlu
Naziye Ak
Nazmiye Yıldırım
Neslihan Cabioğlu
Nilgün Kapucuoğlu
Nuha Abdullah Khomais
Osman Zekioğlu
Serdar Özbaş
Sevgi Canbaz
Shigeru Imoto
Sibel Söylemez
Tibor Tot
Tuba Kayan Tapan
Turkan İkizceli
Yaşar Çöpelci
Yasemin Kayadibi
Yeliz Emine Ersoy
Yeşim Eralp
Zeynep Erdoğan İyigün

2024 Author Index

2024 Author Index

2024 Author Index

2024 Subject Index

2024 Subject Index