Title

Digital mammography and digital breast tomosynthesis for detecting invasive lobular and ductal carcinoma

Journal

Breast Cancer Research and Treatment, 202(3)

ISSN

0167-6806

Authors

Onega, Tracy

Abraham, Linn

Miglioretti, Diana L

et al.

Publication Date

2023-12-01

DOI

10.1007/s10549-023-07051-6

Peer reviewed

HHS Public Access

Author manuscript

Breast Cancer Res Treat. Author manuscript; available in PMC 2024 December 01.

Published in final edited form as:

Breast Cancer Res Treat. 2023 December ; 202(3): 505–514. doi:10.1007/s10549-023-07051-6.

Digital mammography and digital breast tomosynthesis for detecting invasive lobular and ductal carcinoma

Tracy Onega[1], **Linn Abraham**[2], **Diana L. Miglioretti**[2,3], **Christoph I. Lee**[4], **Louise M. Henderson**[5], **Karla Kerlikowske**[6,7], **Anna N.A. Tosteson**[8], **Donald Weaver**[9], **Brian L. Sprague**[10], **Erin J. Aiello Bowles**[2], **Roberta M. diFlorio-Alexander**[11]

[1.]Department of Population Health Sciences, and the Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

[2.]Kaiser Permanente Washington Health Research Institute, Kaiser Permanente Washington, Seattle, WA

[3.]Department of Public Health Sciences, University of California, Davis, CA

[4.]Department of Radiology, University of Washington, and Fred Hutchinson Cancer Center, Seattle WA

[5.]Department of Radiology, University of North Carolina, Chapel Hill, NC

[6.]Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco, CA

[7.]General Internal Medicine Section, Department of Veterans Affairs, University of California, San Francisco, CA

[8.]The Dartmouth Institute for Health Policy and Clinical Practice and Dartmouth Cancer Center, Geisel School of Medicine at Dartmouth, Lebanon, NH

[9.]Department of Pathology, University of Vermont, Burlington, VT

[10.]Departments of Surgery and Radiology, University of Vermont Cancer Center, University of Vermont, Burlington, VT

[11.]Department of Radiology, Dartmouth-Hitchcock Medical Center, Lebanon, NH

Abstract

Purpose: Invasive lobular carcinoma (ILC) is a distinct histological subtype of breast cancer that can make early detection with mammography challenging. We compared imaging performance of

Corresponding address: Tracy Onega, PhD, MS, MA, 2000 Circle of Hope Dr., Huntsman Cancer Institute, RS 4725, Salt Lake City, UT 84018, tracy.onega@hci.utah.edu.

Author Contributions

Conceptualization: TO, DLM, CIL, RMD; Data curation: TO, LA, DLM, CIL, LMH, KK, DW, BLS, EJAB; Formal Analysis: LA, TO, DLM. Methodology: TO, LA, DLM, CIL, LMH, KK, DW, BLS, EJAB, RMD. Supervision: TO. Writing - original draft: TO. Writing - review & editing: TO, LA, DLM, CIL, LMH, KK, DW, BLS, EJAB, RMD.

STATEMENTS AND DECLARATIONS

Competing Interests

There are no other conflicts of interest to disclosure for any of the other authors.

digital breast tomosynthesis (DBT) to digital mammography (DM) for diagnoses of ILC, invasive ductal carcinoma (IDC), and invasive mixed carcinoma (IMC) in a screening population.

Methods: We included screening exams (DM;N=1,715,249 or DBT;N=414,793) from 2011–2018 among 839,801 women in the Breast Cancer Surveillance Consortium. Examinations were followed for one year to ascertain incident ILC, IDC, or IMC. We measured cancer detection rate (CDR) and interval invasive cancer rate/1000 screening examinations for each histological subtype and stratified by breast density and modality. We calculated relative risk (RR) for DM vs. DBT using log-binomial models to adjust for the propensity of receiving DBT vs. DM.

Results: Unadjusted CDR per 1000 mammograms of ILC overall was 0.33 (95%CI 0.30–0.36) for DM; 0.45 (95%CI 0.39–0.52) for DBT, and for women with dense breasts- 0.33 (95%CI 0.29–0.37) for DM and 0.54 (95%CI 0.43–0.66) for DBT. Similar results were noted for IDC and IMC. Adjusted models showed a significantly increased RR for cancer detection with DBT compared to DM among women with dense breasts for all three histologies (RR; 95%CI: ILC 1.53; 1.09–2.14, IDC 1.21; 1.02–1.44, IMC 1.76; 1.30–2.38), but no significant increase among women with non-dense breasts.

Conclusion: DBT was associated with higher CDR for ILC, IDC, and IMC for women with dense breasts. Early detection of ILC with DBT may improve outcomes for this distinct clinical entity.

Keywords

Breast cancer; tomosynthesis; mammography; breast density

INTRODUCTION

Invasive lobular carcinoma (ILC) accounts for 10–15% of invasive breast cancer and is the second most common histologic type of breast cancer after invasive ductal carcinoma (IDC). ILC is characterized by a unique growth pattern due to the loss of E-cadherin, a cell-adhesion protein that is normally present on lobular epithelial cells. The lack of cell adhesion in ILC causes single malignant cells to invade the stroma or encircle the ducts in a linear non-mass pattern. Due to this infiltrative, discohesive tumor growth, ILC is less likely to form a mass lesion, disrupt the underlying breast architecture, or incite a strong desmoplastic reaction. In view of these histologic features ILC is more likely to present on mammography as a subtle asymmetry or architectural distortion rather than as a mass. ILC is also less likely than IDC to be associated with calcifications. These combined imaging features make ILC more difficult to detect on mammography [1, 3–5]. As a result, ILC presents at a later stage than IDC, and interval cancers are more frequent for ILC (19–43% of cases) than for IDC [2,3]. Because of this relative difficulty in detecting ILC, identifying breast imaging modalities that are most effective at early detection is critical to optimizing outcomes for women with ILC.

Digital breast tomosynthesis (DBT) has been shown to have slightly higher cancer detection compared to DM [6–9]. DBT can enhance the visualization of non-calcified masses, asymmetric densities, and architectural distortion, imaging characteristics that are all associated with ILC. Therefore, there is potential for DBT to improve to the detection of

ILC compared to DM [10–13]. A meta-analysis reported a greater detection of ILC (pooled RR: 1.90; 95% CI, 1.21–2.98) when adding DBT to DM [12]. However, this meta-analysis only reported on 65 cases of ILC from four studies and did not estimate performance characteristics of DBT vs. DM beyond cancer detection rate (CDR). A more recent study from a population-based mammography registry did not find any significant difference in detection of ILC compared to invasive ductal cancer (IDC) between DBT and DM; but the study was small and likely underpowered [14]. Our study objective was to compare DM and DBT for detection of ILC in the large, multisite Breast Cancer Surveillance Consortium (BCSC) cohort. We compared CDR, interval invasive cancer rate, and sensitivity for DM and DBT for ILC, IDC, and invasive mixed carcinoma (IMC) – the histology subgroups of the preponderance of invasive cancers.

METHODS

Data Sources, Study Setting, and Study Participants

Data from five Breast Cancer Surveillance Consortium (BCSC) [15] breast imaging registries (Carolina Mammography Registry, Metropolitan Chicago Breast Cancer Registry, New Hampshire Mammography Network, San Francisco Mammography Registry, and Vermont Breast Cancer Surveillance System) that collected DM and DBT screening exam use and radiologist assessments, benign and malignant breast pathology, breast cancer outcomes, and other clinical and sociodemographic characteristics were included in this study. Registries collect data through a combination of women's self-report (socio-demographics, first-degree family history), electronic health records, radiology imaging systems, pathology records, and North American Association of Central Cancer Registries (NAACCR)-affiliated cancer registries. Data from the registries were pooled and analyzed at the Statistical Coordinating Center.

The institutional review boards of the participating BCSC registries and Statistical Coordinating Center (SCC) approved all study activities through passive consent (three registries) or waiver of written consent (two registries and the SCC). This study was Health Insurance Portability and Accountability Act compliant. Registries and the SCC received a federal Certificate of Confidentiality and other protections for the identities of women, physicians, and facilities.

Participants—Women aged 40 and older at the time of a DM or DBT screening mammogram between 2011 and 2018 were included in the study. A mammogram was considered a screening mammogram if the radiologist classified the clinical indication as screening, there was no mammogram within the prior 9 months, and no history of breast cancer or mastectomy. Mammograms were excluded if they did not have at least one year of complete cancer capture. Imaging modality (DM or DBT) was recorded for each exam within the radiology imaging systems.

Study Variables

Histology and Cancer Ascertainment—Cancer type (invasive/in situ) and histology were ascertained by selecting all breast cancers diagnosed within one year after the

screening exam based on linkages with pathology databases and cancer registries. If multiple breast cancer records existed in the following 6 months after the first cancer diagnosis date, then the most severe diagnosis was used (invasive > in situ). If multiple invasive diagnoses were found in that time period then they were compared and the most severe value was used based on the following hierarchy: mixed (ductal and lobular) > ductal > NOS > lobular. Histology was classified as ILC, IDC, and IMC cancers based on pathology reports collected by each BCSC registry using validated abstraction methods as well as cancer registry classification. If a screen was followed by a diagnosis of invasive cancer with histology classified as “Invasive, Not otherwise specified” or “Invasive, Other” (N=88), it was assumed that the invasive cancer was not ILC, IDC, or IMC.

Imaging Performance Measures—We assessed cancer detection rate (CDR) per 1000 screens, interval cancer rate per 1000 screens, and sensitivity (%) using the final assessment of the screening mammogram including all diagnostic work-up of abnormal screens. BI-RADS assessments of 1 (negative) or 2 (benign finding) were considered negative and assessments of 3 (probably benign finding), 4 (suspicious abnormality), or 5 (highly suggestive of malignancy) were considered positive. If the initial assessment based on the screening exam was 0 (additional imaging evaluation is needed), then the mammogram was followed for 90 days to determine the final assessment after diagnostic imaging using previously described methods [16]. If after 90 days a non-BI-RADS 0 assessment could not be ascertained (<0.6% of screening mammograms), then the final result was imputed based on age, type of mammogram, BCSC registry, facility, reader, and cancer outcome. CDR was defined as the number of positive screening exams with invasive carcinoma by histology * 1000 divided by the total number of screening exams. Interval invasive cancer was defined as the number of negative screening exams with invasive carcinoma within 12 months * 1000 divided by the total number of screening exams. Sensitivity was defined as the number of positive screening exams with invasive carcinoma * 100 divided by the number of screening exams with invasive carcinoma. A screen-detected cancer was defined as a cancer that was preceded by a positive screening exam within 12 months.

Covariates—We adjusted for woman-level factors, specifically: age, race/ethnicity, BI-RADS breast density, menopausal status, current hormone therapy (HT) use, time since last mammogram, first degree family history of breast cancer, and prior benign breast biopsy. Age in years at the time of the screening exam was categorized as: 40–49, 50–59, 60–69, 70–74, 75+. Race and ethnicity were self-reported as: Hispanic/Latina or non-Hispanic/non-Latina Asian/Pacific Islander, Black, White, and Other/Unknown, which included American Indian, Alaskan Native, multiracial, Other, and Unknown. BI-RADS breast density (taken at the time of exam or within 18 months of the exam) was classified as dense (heterogeneously or extremely dense) or non-dense (almost entirely fatty or scattered fibroglandular densities). Women were considered postmenopausal if they reported they had natural menopause, had both ovaries removed, were 60 years of age or older, or if the only information available was that their last menstrual period was more than 365 days prior. History of benign biopsy was collected from both self-report and pathology databases.

Statistical Analysis

We described characteristics of screening mammograms by imaging modality and invasive carcinoma histology. Performance characteristics of DM and DBT were calculated for each histology using screening mammogram as the unit of analysis. Specifically, unadjusted rates for CDR, Interval cancer rate, and sensitivity were calculated for ILC, IDC, and IMC, both overall and stratified by density. Propensity scores for screening with DBT vs. DM were estimated from a logistic regression model that included BCSC registry, year of mammogram, age, age-squared, density, time since last mammogram, family history of breast cancer, race/ethnicity, prior benign biopsy and postmenopausal women with HT use or without HT use (or with unknown HT use). For comparing DBT vs. DM for each performance measure, the unadjusted and adjusted relative risks were estimated using log-binomial models and the absolute risk differences were estimated using generalized linear models with identity link and binomial distribution. Models were fit using generalized estimating equations to account for correlation within facilities. Adjusted models included the propensity score. Analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC).

RESULTS

The study population included 2,130,042 screening mammograms performed on 839,801 women, 1,715,249 (80.5%) of which were DM and 414,793 (19.5%) of which were DBT (Table 1). In total, there were 9,099 screening exams with ILC, IDC, or IMC diagnosed within 1 year (ILC: 10.0%, IDC: 82.9%; IMC: 7.1%) (Table 2) The highest frequency of DBT use was among screens with a diagnosis of IMC (27.2%), followed by ILC (23.5%) and IDC (20.2%) (Supplemental Table 1). Characteristics of women at the time of screening did not vary notably by imaging modality used, with the exception of race; a higher proportion of white women received DBT versus DM, while for other races and Hispanic ethnicity, DM was more frequent (Table 1). The median age for women at the time of screening was the same for both DM and DBT (58 years, interquartile range (IQR), 50–66 years), but women with an invasive carcinoma, particularly ILC, were older (in years: ILC: 65, IQR 56–71; IDC: 62, IQR 54–70; IMC: 63, IQR 54–71) than women without a breast cancer diagnosis. Women with ILC were more likely to be postmenopausal, use HT, and have a prior benign breast biopsy compared to women with IDC or IMC (Table 2). We examined the characteristics of women at the time of screening by histology and mode of detection (screen-detected or interval cancer) and the expected pattern of larger tumor size for interval- vs. screen-detected was seen for ILC, IDC, and IMC. However, for ILC detection, a higher proportion of smaller tumors (<=10 mm and 11–20 mm) were found with DBT compared to DM

The CDRs for ILC, IDC, and IMC were higher for DBT vs. DM among all screens (dense and non-dense combined), among screens performed on women with dense breasts, but not in screens performed on women with non-dense breasts (Table 3). Unadjusted ILC detection rates were similar for DM vs. DBT for screens in women with non-dense breasts (DM: 0.33 per 1000, 95% CI 0.29–0.37 vs. DBT: 0.38, 95% CI 0.31–0.47), but the difference was significant for dense breasts (unadjusted CDR for ILC: 0.33, 95% CI 0.29–0.37 with

DM; 0.54, 95% CI 0.43–0.66 with DBT). (Table 3) Similar patterns were also noted for IDC and IMC. In women with dense breasts, unadjusted sensitivity for ILC was higher for DBT compared to DM (84.3, 95% CI 76.0–90.6 DBT vs. 73.4, 95% CI 68.1–78.1 DM) (Table 3). Interval invasive cancer rates did not differ significantly between DM and DBT for any of the three histologies.

In fully adjusted models for relative risk of each performance measure comparing DBT to DM, we found a significantly higher probability of cancer detection with DBT for all three histology subtypes, but only among screens performed in women with dense breasts. (Table 4). For ILC detection, the relative risk (RR) for CDR comparing DBT to DM was 1.31 (95% CI 1.03–1.65) among all screens and 1.53 (95% CI 1.09–2.14) among screens in women with dense breasts, with an absolute risk difference of 0.11 (95% CI 0.01–0.20) among all screens and 0.19 (95% CI 0.03–0.35) among screens in women with dense breasts (Table 4). For IDC and IMC, the relative risk for CDR comparing DBT to DM was only significant within screens in women with dense breasts (RR: IDC: 1.21, 95% CI 1.02–1.44, absolute risk difference 0.58, 95% CI 0.05–1.11; RR: IMC: 1.76, 95% CI 1.30–2.38; absolute risk difference 0.19, 95% CI 0.09–0.29) (Table 4). Relative risk for sensitivity was only significantly higher for DBT compared to DM for IMC, and most notably for screens in women with dense breasts (RR: 1.21 95% CI 1.11–1.32, absolute risk difference 13.77, 95% CI 4.04–23.50) (Table 4).

DISCUSSION

This is the largest study to date comparing the screening performance of DBT vs. DM in detection of lobular, ductal, or mixed invasive carcinoma histological subtypes in a generalizable population, both overall and stratified by breast density. We found that CDR was significantly higher for DBT compared to DM for ILC, IMC, and IDC, even when adjusting for potential confounders and selection bias. The improved performance of DBT over DM for CDR, and sensitivity in the case of IMC, was observed almost exclusively among women with dense breasts; and for CDR, most notably for ILC. The overall, and dense-breasts-only estimates for higher CDR with DBT vs. DM were significant, but those for women with non-dense breasts were not. Thus, the reported improvement in performance with DBT may be attributed to higher cancer detection in dense breast tissue.

For ILC, the improved CDR with DBT vs. DM is likely to have a greater clinical impact, given that it is more likely to be occult on traditional 2D DM than other histology subtypes. [17]. Further, it is now accepted that lobular subtypes of breast cancer are distinct in their morphology, biology, clinical behaviors, and prognoses [17]. ILC is more likely to be larger at the time of detection and is predominantly estrogen receptor positive and HER2 negative. Compared to IDC, or invasive breast cancer of no special type, ILC is more likely to be multicentric or multifocal and more likely to have nodal and distant metastases, therefore presenting at later stage than IDC despite lower grade. Long term outcomes for ILC are inferior to stage-matched IDC, and the ability to improve detection of ILC is therefore clinically relevant [18–21] Randomized clinical trials are currently underway to test neoadjuvant chemotherapy and endocrine therapies targeting specific molecular profiles

found in ILC, to move away from a ‘one-size-fits-all’ approach to targeted approaches recognizing ILC as a distinct disease process. [22–28]

In this study, we found the most significantly improved performance measure for DBT over DM was cancer detection, which was about 76%, 53%, and 21% more likely to be detected for IMC, ILC, and IDC, respectively, in women with dense breasts. Notably, we did not find a significant decrease in interval cancers.

Studies comparing DBT to DM for detecting invasive lobular vs. invasive ductal histology, have yielded both positive and negative results. In a small Italian study, ILC was found to be significantly more conspicuous on DBT than on DM [5]. However, another small study, in Vermont, found no significant difference in detection of ILC, IMC, or IDC using DBT vs. DM [14]. While the latter study was population-based and included over 86,000 DBT exams (and >97,000 DM exams), the state of Vermont, in which it was conducted, is relatively homogenous and had only recently adopted DBT in about half of its facilities [14]. Our study had the benefit of millions of exams with a longer period in which DBT uptake occurred; thus providing the most robust evidence to date for better cancer detection with DBT vs. DM overall, and notably for ILC and IMC.

To our knowledge, we are the first to report on DBT vs. DM performance measures for invasive breast cancer histology subtypes by breast density. Our findings make a compelling argument for attributing DBT’s improved cancer detection rates in women with dense breasts, particularly for ILC and IMC. A prior study in the BCSC examined DBT vs. DM performance in relation to the four BI-RADS breast density categories [8]. Those results showed better CDRs with DBT compared to DM for scattered fibroglandular and heterogeneously dense breasts, but not for entirely fatty or extremely dense. For example, among women age 40–79 years with heterogeneously dense breasts cancer detection increased from 3.7 with DM to 5.3 with DBT (RR, 1.42; 95% CI, 1.23–1.64) on exams that were not baseline; those exams showed even more notably increased CDRs. Because we were examining the relatively rare outcomes of ILC and IMC in a screening population, we dichotomized breast density. Nevertheless, our observed effect of dense breasts on improved CDR for ILC and IMC for DBT vs. DM points to a robust effect that is not diluted by dichotomizing as we did. Thus, as mammography performance with DBT is becoming implemented as the primary screening modality, its greatest impact may be among women with dense breasts. However, we note that impacts on morbidity and mortality based on increased CDR with DBT screening are still uncertain, given the potential to diagnose more indolent tumors without a reduction in interval cancers which tend to be aggressive.

Our study had many strengths and also several limitations. A strength is the unparalleled ability of the BCSC to study DBT performance in relation to specific invasive breast cancer histology subtypes and also by breast density. This required a very large sample size, high-quality case ascertainment and follow-up, and breast density measures, all of which the BCSC contains. By using this large nationally-representative population, we are able to overcome previous limitations of sparse reporting of performance measures, low number of ILC observations, limited generalizable practice settings, and the absence of subgroup analyses in prior studies. A limitation we faced, despite our very large numbers of screening

exams, was the inability to examine the four-category BI-RADS breast density measures separately. Evaluating four, instead of two, breast density categories was not feasible for maintaining adequate cell size, given the relative rarity of ILC and IMC. Nevertheless, this study provides evidence for improved cancer detection using DBT vs. DM for ILC and IMC.

Invasive breast cancers of lobular, ductal, and mixed lobular/ductal histology are more likely to be detected using DBT, particularly for women with heterogeneously dense and extremely dense breasts, but interval cancers rates are similar for the two modalities. Currently there are no risk models to predict invasive lobular cancer, so women at high risk who may benefit from alternative screening strategies cannot be identified. Early detection of ILC may help reduce the morbidity and mortality burden of this clinical entity that is increasingly recognized as distinct in its molecular and clinical profile with poor long-term outcomes compared to IDC. Ultimately, until effective targeted treatment approaches for ILC management become known, earlier detection remains paramount for optimizing outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

The collection of cancer and vital status data used in this study was supported in part by several state public health departments and cancer registries throughout the U.S. For a full description of these sources, please see: https://www.bcsc-research.org/about/work-acknowledgement. All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee, nor those of the National Cancer Institute or the National Institutes of Health. We thank the participating women, mammography facilities, and radiologists for the data they have provided for this study. You can learn more about the BCSC at: http://www.bcsc-research.org/.

The collection of cancer incidence and vital status data used in this study was supported, in part, by:

• The California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement U58-DP003862-01 awarded to the California Department of Public Health;

• The Vermont Cancer Registry, supported in part by Cooperative Agreement NU58DP006322 from the Centers for Disease Control and Prevention, awarded to the Vermont State Agency of Human Services.

• The Cancer Surveillance System of the Fred Hutchinson Cancer Research Center, which is funded by contracts N01-CN-005230, N01-CN-67009, N01-PC-35142, HHSN261201000029C, and HHSN2612013000012I from the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute with additional support from the Fred Hutchinson Cancer Research Center and the State of Washington;

• The New Hampshire State Cancer Registry supported in part by cooperative agreement U55/CCU-121912 awarded to the New Hampshire Department of Health and Human Services, Division of Public Health Services, Bureau of Disease Control and Health Statistics, Health Statistics and Data Management Section;

• The North Carolina Central Cancer Registry, which is partially supported by the Centers for Disease Control and Prevention under cooperative agreement DP12-120503CONT14;

• Manuscripts including data from the Metro Chicago Breast Cancer Registry were supported in part by the Illinois Department of Public Health, Illinois State Cancer Registry which is partially supported by the Centers for Disease Control and Prevention under cooperative agreement DP12-120504CONT15.

The ideas and opinions expressed herein are those of the authors and endorsement by the State of California, the California Department of Public Health; Illinois Department of Public Health; New Hampshire Department of Health and Human Services; the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred.

We thank the participating women, mammography facilities, and radiologists for the data they have provided for this study.

Funding

This work was supported by the Breast Cancer Surveillance Consortium with funding from the National Cancer Institute (P01CA154292, U54CA163303, R01CA149365, R50CA211115) and the Agency for Health Research and Quality (R01 HS018366–01A1). Data collection for this research was additionally funded through a Patient-Centered Outcomes Research Institute (PCORI) Program Award (PCS-1504–30370).

The National Cancer Institute had no role in the study's design; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. Likewise, the content in this manuscript is solely the responsibility of the authors and does not necessarily represent the views of PCORI, its Board of Governors or Methodology Committee.

Conflicts of Interest Disclosures

C.I. Lee receives personal fees from the American College of Radiology for journal editorial board work and textbook royalties from UpToDate, Inc., Oxford University Press, and McGraw Hill, Inc.

Data Availability

Data :: BCSC (bcsc-research.org)

Data collected and maintained by the Breast Cancer Surveillance Consortium are protected by a Federal Certificate of Confidentiality from the National Institutes of Health (NIH). Per the terms of this certificate, identifiable data shall be disclosed only when: required by federal, state, or local laws; necessary for medical treatment of the individual to whom the data pertains; made with the consent of the individual; or made for the purposes of other scientific research complying with federal regulations governing human subjects research. For more details on these protections and their limits, please visit the NIH Certificate of Confidentiality Website.

REFERENCES

1. Mouabbi JA, Hassan A, Lim B. et al. Invasive lobular carcinoma: an understudied emergent subtype of breast cancer. Breast Cancer Res Treat 2022. 193, 253–264 10.1007/s10549-022-06572-w [PubMed: 35347549]
2. Johnson K, Sarma D, Hwang ES. Lobular breast cancer series: imaging. Breast Cancer Res. 2015;17:94 [PubMed: 26163296]
3. Porter AJ, Evans EB, Foxcroft LM, et al. Mammographic and ultrasound features of invasive lobular carcinoma of the breast. Journal of Medical Imaging and Radiation Oncology. 2013;5(1)
4. McCart Reed AE, Kalinowski L, Simpson PT, et al. Invasive lobular carcinoma of the breast: the increasing importance of this special subtype. Breast Cancer Research and Treatment. 2021. 23:6. 10.1186/s13058-020-01384-6
5. Romanucci G, Zantedeschi L, Ventriglia A, et al. Lobular Breast Cancer Conspicuity on Digital Breast Tomosynthesis Compared to Synthesized 2D Mammography: A Multireader Study. Journal of Imaging. 2021; 7(9):185. 10.3390/jimaging7090185 [PubMed: 34564111]

6. McDonald ES, Oustimov A, Weinstein SP, et al. Effectiveness of Digital Breast Tomosynthesis Compared With Digital Mammography: Outcomes Analysis From 3 Years of Breast Cancer Screening. JAMA Oncol. 2016;2(6):737–743. doi:10.1001/jamaoncol.2015.5536 [PubMed: 26893205]
7. Alabousi M, Wadera A, Kashif Al-Ghita M, et al. , Performance of digital breast tomosynthesis, synthetic f¢mammography, and digital mammography in breast cancer screening: a systematic review and meta-analysis. JNCI: Journal of the National Cancer Institute, 2021.113(6), 680–690. [PubMed: 33372954]
8. Lowry KP, Coley RY, Miglioretti DL, et al. Screening performance of digital breast tomosynthesis vs digital mammography in community practice by patient age, screening round, and breast density. JAMA Network open, 2021.3(7), e2011792-e2011792.
9. Kerlikowske K, Su Y, Sprague BL, et al. Association of Screening With Digital Breast Tomosynthesis vs Digital Mammography With Risk of Interval Invasive and Advanced Breast Cancer. JAMA. 2022;327(22):2220–2230. doi:10.1001/jama.2022.7672 [PubMed: 35699706]
10. Menezes GLG, van den Bosch MAAJ, Postma EL, et al. Invasive ductolobular carcinoma of the breast: spectrum of mammographic, ultrasound and magnetic resonance imaging findings correlated with proportion of the lobular component. SpringerPlus. 2013;2:621. [PubMed: 24340243]
11. Chammings F, Kao E, Ladis A, et al. Imagine features and conspicuity of invasive lobular carcinomas on digital breast tomosynthesis. British Journal of Radiology. 2017;90:20170128.
12. Grubstein A, Rapson Y, Morgenstern S, et al. Invasive lobular carcinoma of the breast: appearance on digital breast tomosynthesis. Breast Care. 2016;11:359–362. [PubMed: 27920631]
13. Mariscotti G, Durando M, Houssami N, et al. Digital breast tomosynthesis as an adjunct to digital mammography for detecting and characterising invasive lobular cancers: a multi-reader study. Clinical Radiology. 2016;71(9):889–95. [PubMed: 27210245]
14. Yun SJ, Ryu CW, Rhee SJ, et al. Benefit of adding digital breast tomosynthesis to digital mammography for breast cancer screening focused on cancer characteristics: a meta-analysis. Breast Cancer Research Treatment. 2017;164:557–569. [PubMed: 28516226]
15. Fuji MH, Herschorn SD, Sowden M, et al. Detection rates for benign and malignant diagnoses on breast cancer screening with digital breast tomosynthesis in a statewide mammography registry study. AJR. American journal of roentgenology, 2019. 212(3), 706. [PubMed: 30673339]
16. Breast Cancer Surveillance Consortium. About the BCSC :: BCSC (bcsc-research.org). Last accessed: 7/31/2022.
17. Breast Cancer Surveillance Consortium. Standard Definitions :: BCSC (bcsc-research.org). Last accessed: 7/31/2022.
18. Arpino G, Bardou VJ, Clark GM, et al. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. Breast Cancer Res. 2004;6(3):R149–56. Da Ros L, Moretti A, Querzoli P, et al. HER2-positive lobular versus ductal carcinoma of the breast: pattern of first recurrence and molecular insights. Clin Breast Cancer. 2018;18(5):e1133–9. [PubMed: 15084238]
19. Christgen M, Gluz O, Harbeck N, et al. Differential impact of prognostic parameters in hormone receptor-positive lobular breast cancer. Cancer. 2020;126(22):4847–58. [PubMed: 32780421]
20. Flores-Diaz D, Arce C, Flores-Luna L, et al. Impact of invasive lobular carcinoma on long-term outcomes in Mexican breast cancer patients. Breast Cancer Res Treat. 2019;176(1):243–9. [PubMed: 30997623]
21. Altundag K. HER2+ and triple-negative phenotypes in invasive lobular carcinoma might have different specific biological features. Breast Cancer Res Treat. 2019;176(3):719. [PubMed: 31104173]
22. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med. 2018;379(20):1926–36. [PubMed: 30345905]
23. Palbociclib and Endocrine Therapy for LObular Breast Cancer Preoperative Study (PELOPS) United states: National library of Medicine; 2016 [Available from: https://clinicaltrials.gov/ct2/show/NCT0276454. Accessed Oct 2020.

24. Assessing Efficacy of Carboplatin and ATezOlizumab in Metastatic Lobular Breast Cancer (GELATO) Netherlands2017 Available from: https://clinicaltrials.gov/ct2/show/NCT03147040. Accessed Oct 2020.
25. ROS1 Targeting With Crizotinib in Advanced E-cadherin Negative, ER Positive Lobular Breast Cancer or Diffuse Gastric Cancer Study (ROLo) United Kingdom2019 [Available from: https://clinicaltrials.gov/ct2/show/NCT0362064. Accessed Oct 2020.
26. Neoadjuvant Study of Targeting ROS1 in Combination With Endocrine Therapy in Invasive Lobular Carcinoma of the Breast (ROSALINE) [available from https://clinicaltrials.gov/ct2/show/NCT04551495]. Accessed Oct 2020.
27. Perez-Garcia J, Cortes J, Metzger-Filho O. Efficacy of single-agent chemotherapy for patients with advanced invasive lobular carcinoma: a pooled analysis from three clinical trials. Oncologist. 2019;24(8):1041–7. [PubMed: 30578311]
28. Ruhstaller T, Giobbie-Hurder A, Colleoni M, et al. Adjuvant letrozole and tamoxifen alone or sequentially for postmenopausal women with hormone receptor-positive breast cancer: long-term follow-up of the BIG 1–98 trial. J Clin Oncol. 2019;37(2):105–14. [PubMed: 30475668]
29. Metzger-Filho O, Ferreira AR, Jeselsohn R, et al. Mixed Invasive Ductal and Lobular Carcinoma of the Breast: Prognosis and the Importance of Histologic Grade. Oncologist. 2019 Jul;24(7):e441–e449. doi: 10.1634/theoncologist.2018-0363. Epub 2018 Dec 5. PMID: 30518616; PMCID: PMC6656459. [PubMed: 30518616]
30. Hogan MP, Amir T, Sevilimedu V, et al. AJR Am J Roentgenol. 2021 June; 216(6): 1486–1491. doi:10.2214/AJR.20.23480. [PubMed: 33787291]
31. Kerlikowske K, Su Y, Sprague BL, et al. Association of Screening With Digital Breast Tomosynthesis vs Digital Mammography With Risk of Interval Invasive and Advanced Breast Cancer. JAMA. 2022;327(22):2220–2230. doi:10.1001/jama.2022.7672 [PubMed: 35699706]

Table 1.

Woman-level characteristics of screening mammograms using digital mammography (DM) or digital breast tomosynthesis (DBT)

	Screening Mammogram	
	DM N (%)	**DBT N (%)**
Total [1]	1715249	414793
Age (years)		
40–49	421592 (24.6)	98795 (23.8)
50–59	537516 (31.3)	133618 (32.2)
60–69	463538 (27.0)	116526 (28.1)
70–74	142557 (8.3)	35929 (8.7)
75+	150046 (8.7)	29925 (7.2)
BI-RADS density		
Almost entirely fatty	158493 (10.0)	43000 (10.7)
Scattered fibroglandular densities	718055 (45.2)	190792 (47.4)
Heterogeneously dense	598046 (37.7)	141738 (35.2)
Extremely dense	112793 (7.1)	27382 (6.8)
Menopausal status [2]		
Postmenopausal	994739 (63.7)	243463 (67.9)
Pre-menopausal	486095 (31.1)	96481 (26.9)
Hormone therapy use		
No	1433889 (94.8)	340323 (92.3)
Yes	78477 (5.2)	28542 (7.7)
Time since last mammogram		
Within 2 years (9–30 months)	1390230 (85.3)	351071 (87.9)
3–4 years (>30–59 months)	93155 (5.7)	21426 (5.4)
5 years or more or first mammogram	147291 (9.0)	27092 (6.8)
First degree family history of breast cancer		
No	1390015 (83.8)	307603 (79.7)
Yes	269688 (16.2)	78167 (20.3)
Race/ethnicity		
White	1068455 (62.3)	341563 (82.3)
Black	191575 (11.2)	27104 (6.5)
Asian/Pacific Islander	243713 (14.2)	16337 (3.9)
Hispanic/Latina	112282 (6.5)	13139 (3.2)
Other,Unknown[3]	99224 (5.8)	16650 (4.0)
Prior benign biopsy		
None, Unknown	1368300 (79.8)	322168 (77.7)
Biopsy, pathology unknown	225769 (13.2)	44596 (10.8)
Non-proliferative	86510 (5.0)	33005 (8.0)
Proliferative without atypia	28226 (1.6)	12011 (2.9)

	Screening Mammogram	
	DM N (%)	**DBT N (%)**
Proliferative with atypia	5384 (0.3)	2509 (0.6)
LCIS	1060 (0.1)	504 (0.1)

[1]Missing/Unknown: BI-RADS density: 7.5% DM, 2.9% DBT; Menopausal status: 8.9% DM, 13.6% DBT; Hormone therapy (HT) use: 11.8% DM, 11.1% DBT; Time since last mammogram: 4.9% DM, 3.7% DBT; First degree family history of breast cancer: 3.2% DM, 7.0% DBT

[2]5.2% of women with DM and 5.2% of women with DBT reported surgical menopause.

[3]Includes American Indian, Alaskan Native, Mixed, Other, Unknown

Table 2.

Characteristics of women undergoing screening with a diagnosis of invasive lobular (ILC), ductal (IDC), or mixed (IMC) carcinoma

	Invasive Lobular Carcinoma (ILC)	Invasive Ductal Carcinoma (IDC)	Invasive Mixed (IMC)
	N (%)	N (%)	N (%)
Total	912	7543	644
Age (years)			
40–49	102 (11.2)	1156 (15.3)	86 (13.4)
50–59	197 (21.6)	1975 (26.2)	160 (24.8)
60–69	332 (36.4)	2402 (31.8)	220 (34.2)
70–74	135 (14.8)	961 (12.7)	85 (13.2)
75+	146 (16.0)	1049 (13.9)	93 (14.4)
BI-RADS density			
Almost entirely fatty	53 (6.2)	545 (7.8)	40 (6.8)
Scattered fibroglandular densities	375 (43.9)	3281 (47.1)	257 (43.4)
Heterogeneously dense	366 (42.8)	2703 (38.8)	254 (42.9)
Extremely dense	61 (7.1)	441 (6.3)	41 (6.9)
Menopausal status			
Postmenopausal	693 (80.1)	5271 (75.2)	455 (78.6)
Pre-menopausal	152 (17.6)	1431 (20.4)	104 (18.0)
Hormone therapy use			
No	674 (90.0)	5751 (93.5)	468 (90.5)
Yes	75 (10.0)	401 (6.5)	49 (9.5)
Time since last mammogram			
Within 2 years (9–35 months)	710 (82.0)	5600 (78.8)	497 (80.7)
3–4 years (36–59 months)	75 (8.7)	600 (8.4)	43 (7.0)
5 years or more or first mammogram	81 (9.4)	905 (12.7)	76 (12.3)
First degree family history of breast cancer			
No	657 (74.8)	5446 (75.9)	460 (75.3)
Yes	221 (25.2)	1733 (24.1)	151 (24.7)
Race/ethnicity			
White, non-Hispanic	710 (77.9)	5287 (70.1)	535 (83.1)
Black, non-Hispanic	94 (10.3)	903 (12.0)	34 (5.3)
Asian/Pacific Islander	57 (6.3)	765 (10.1)	35 (5.4)
Hispanic	27 (3.0)	298 (4.0)	12 (1.9)
Other, Unknown[2]	24 (2.6)	290 (3.8)	28 (4.3)
Prior benign biopsy			
None, Unknown	584 (64.0)	5359 (71.0)	442 (68.6)
Biopsy, pathology unknown	200 (21.9)	1381 (18.3)	118 (18.3)
Non-proliferative	76 (8.3)	532 (7.1)	51 (7.9)
Proliferative without atypia	32 (3.5)	199 (2.6)	22 (3.4)

	Invasive Lobular Carcinoma (ILC)	Invasive Ductal Carcinoma (IDC)	Invasive Mixed (IMC)
	N (%)	N (%)	N (%)
Proliferative with atypia	11 (1.2)	64 (0.8)	8 (1.2)
LCIS	9 (1.0)	8 (0.1)	3 (0.5)

[1]Missing/Unknown: BI-RADS density: 6.3% ILC, 7.6% IDC, 8.1% Mixed; Menopausal status: 5.2% ILC, 7.1% IDC, 10.1% Mixed; Hormone therapy (HT) use:17.9% ILC, 18.4% IDC, 19.7% Mixed; Time since last mammogram: 5.0% ILC, 5.8% IDC, 4.3% Mixed; First degree family history of breast cancer: 3.7% ILC, 4.8% ILC, 5.1% Mixed

[2]Surgical menopause was reported in 2.3% of women with ILC, 4.4% with IDC, and 3.5% with IMC.

[3]Includes American Indian, Alaskan Native, Mixed, Other, Unknown

Breast Cancer Res Treat. Author manuscript; available in PMC 2024 December 01.

Table 3.

Performance measures of digital screening mammography (DM) compared to digital breast tomosynthesis (DBT) for detection of invasive lobular (ILC) or ductal (IDC) carcinoma, overall and by breast density.

ILC		DM			DBT	
Performance Measure	**Events**	**Exams**	**Unadjusted rate**	**Events**	**Exams**	**Unadjusted rate**
Overall*			**Estimate (95% CI)**			**Estimate (95% CI)**
CDR per 1000 exams	564	1715249	0.33 (0.30, 0.36)	188	414793	0.45 (0.39, 0.52)
Interval cancer rate per 1000 exams	134	1715249	0.08 (0.07, 0.09)	26	414793	0.06 (0.04, 0.09)
Sensitivity	564	698	80.8 (77.7, 83.7)	188	214	87.9 (82.7, 91.9)
Non-dense breasts**						
CDR per 1000 exams	291	876548	0.33 (0.29, 0.37)	89	233792	0.38 (0.31, 0.47)
Interval cancer rate per 1000 exams	39	876548	0.04 (0.03, 0.06)	9	233792	0.04 (0.02, 0.07)
Sensitivity	291	330	88.2 (84.2, 91.5)	89	98	90.8 (83.3, 95.7)
Dense breasts***						
CDR per 1000 exams	234	710839	0.33 (0.29, 0.37)	91	169120	0.54 (0.43, 0.66)
Interval cancer rate per 1000 exams	85	710839	0.12 (0.10, 0.15)	17	169120	0.10 (0.06, 0.16)
Sensitivity	234	319	73.4 (68.1, 78.1)	91	108	84.3 (76.0, 90.6)
IDC		**DM**			**DBT**	
Performance Measure	**Events**	**Exams**	**Unadjusted rate**	**Events**	**Exams**	**Unadjusted rate**
Overall*			**Estimate (95% CI)**			**Estimate (95% CI)**
CDR per 1000 exams	5177	1715249	3.02 (2.94, 3.10)	1323	414793	3.19 (3.02, 3.37)
Interval cancer rate per 1000 exams	844	1715249	0.49 (0.46, 0.53)	199	414793	0.48 (0.42, 0.55)
Sensitivity	5177	6021	86.0 (85.1, 86.9)	1323	1522	86.9 (85.1, 88.6)
Non-dense breasts**						
CDR per 1000 exams	2759	876548	3.15 (3.03, 3.27)	728	233792	3.11 (2.89, 3.35)
Interval cancer rate per 1000 exams	266	876548	0.30 (0.27, 0.34)	73	233792	0.31 (0.24, 0.39)
Sensitivity	2759	3025	91.2 (90.1, 92.2)	728	801	90.9 (88.7, 92.8)

Dense breasts ***						
CDR per 1000 exams	1957	710839	2.75 (2.63, 2.88)	543	169120	3.21 (2.95, 3.49)
Interval cancer rate per 1000 exams	520	710839	0.73 (0.67, 0.80)	124	169120	0.73 (0.61, 0.87)
Sensitivity	1957	2477	79.0 (77.3, 80.6)	543	667	81.4 (78.2, 84.3)
Mixed		**DM**			**DBT**	
Performance Measure	**Events**	**Exams**	**Unadjusted rate**	**Events**	**Exams**	**Unadjusted rate**
Overall *			**Estimate (95% CI)**			**Estimate (95% CI)**
CDR per 1000 exams	389	1715249	0.23 (0.20, 0.25)	152	414793	0.37 (0.31, 0.43)
Interval cancer rate per 1000 exams	80	1715249	0.05 (0.04, 0.06)	23	414793	0.06 (0.04, 0.08)
Sensitivity	389	469	82.9 (79.2, 86.2)	152	175	86.9 (80.9, 91.5)
Non-dense breasts **						
CDR per 1000 exams	202	876548	0.23 (0.20, 0.26)	65	233792	0.28 (0.21, 0.35)
Interval cancer rate per 1000 exams	23	876548	0.03 (0.02, 0.04)	7	233792	0.03 (0.01, 0.06)
Sensitivity	202	225	89.8 (85.1, 93.4)	65	72	90.3 (81.0, 96.0)
Dense breasts ***						
CDR per 1000 exams	148	710839	0.21 (0.18, 0.24)	78	169120	0.46 (0.36, 0.58)
Interval cancer rate per 1000 exams	53	710839	0.07 (0.06, 0.10)	16	169120	0.09 (0.05, 0.15)
Sensitivity	148	201	73.6 (67.0, 79.6)	78	94	83.0 (73.8, 89.9)

* includes mammograms missing breast density

** density=almost entirely fatty, scattered fibroglandular density

*** density=heterogeneously dense, extremely dense

Table 4.

Performance measures of screening mammography with digital breast tomosynthesis (DBT) compared to digital mammography (DM) for detection of invasive lobular (ILC), ductal (IDC), or mixed (IMC) carcinoma, overall and by breast density.

Performance Measure	DBT v. DM	
ILC		
Overall*	**Relative Risk[1] (95% CI)**	**Absolute Risk Difference[2] (95% CI)**
CDR per 1000 exams	**1.31 (1.03, 1.65)**	**0.11 (0.01, 0.20)**
Interval cancer rate per 1000 exams	0.85 (0.50, 1.46)	−0.01 (−0.05, 0.02)
Sensitivity	1.06 (0.98, 1.15)	4.98 (−1.70, 11.66)
Non-dense breasts**		
CDR per 1000 exams	1.13 (0.89, 1.45)	0.04 (−0.05, 0.13)
Interval cancer rate per 1000 exams	1.18 (0.57, 2.47)	0.01 (−0.02, 0.03)
Sensitivity	0.99 (0.92, 1.06)	−0.98 (−7.32, 5.36)
Dense breasts***		
CDR per 1000 exams	**1.53 (1.09, 2.14)**	**0.19 (0.03, 0.35)**
Interval cancer rate per 1000 exams	0.77 (0.38, 1.53)	---
Sensitivity	1.13 (0.98, 1.29)	9.87 (−1.42, 21.16)
IDC		
Overall*	**Relative Risk[1] (95% CI)**	**Absolute Risk Difference[2] (95% CI)**
CDR per 1000 exams	1.10 (1.00, 1.21)	0.30 (−0.01, 0.60)
Interval cancer rate per 1000 exams	1.03 (0.81, 1.31)	0.01 (−0.11, 0.13)
Sensitivity	1.01 (0.97, 1.04)	0.66 (−2.39, 3.72)
Non-dense breasts**		
CDR per 1000 exams	1.04 (0.91, 1.18)	0.11 (−0.30, 0.53)
Interval cancer rate per 1000 exams	1.07 (0.75, 1.52)	0.02 (−0.10, 0.13)
Sensitivity	1.00 (0.96, 1.03)	−0.31 (−3.46, 2.85)
Dense breasts***		
CDR per 1000 exams	**1.21 (1.02, 1.44)**	**0.58 (0.05, 1.11)**
Interval cancer rate per 1000 exams	1.04 (0.74, 1.46)	0.03 (−0.21, 0.28)
Sensitivity	1.03 (0.97, 1.09)	2.23 (−2.40, 6.86)
Mixed		
Overall*	**Relative Risk[1] (95% CI)**	**Absolute Risk Difference[2] (95% CI)**
CDR per 1000 exams	1.37 (0.99, 1.90)	0.10 (0.00, 0.19)

Interval cancer rate per 1000 exams	0.92 (0.54, 1.54)	---
Sensitivity	**1.09 (1.02, 1.17)**	6.87 (0.98, 12.77)
Non-dense breasts **		
CDR per 1000 exams	1.05 (0.75, 1.47)	0.02 (−0.07, 0.11)
Interval cancer rate per 1000 exams	0.95 (0.44, 2.03)	−0.00 (−0.02, 0.02)
Sensitivity	1.01 (0.93, 1.10)	0.96 (−6.59, 8.52)
Dense breasts ***		
CDR per 1000 exams	**1.76 (1.30, 2.38)**	**0.19 (0.09, 0.29)**
Interval cancer rate per 1000 exams	0.91 (0.44, 1.86)	---
Sensitivity	**1.21 (1.11, 1.32)**	**13.77 (4.04, 23.50)**

[1]Relative risk was estimated based on log-binomial models adjusting for propensity score and correlation within facility.

[2]Absolute risk difference was based on generalized linear models with identity link and binomial distribution adjusting for propensity score and correlation within facility.

*includes mammograms missing breast density

**density=almost entirely fatty, scattered fibroglandular density

***density=heterogeneously dense, extremely dense