

UC Davis

UC Davis Electronic Theses and Dissertations

Title

Benign Breast Disease and Breast Cancer Risk: Implications for Risk Assessment and Clinical Interpretation

Permalink

<https://escholarship.org/uc/item/6kg5d5wv>

ISBN

9798189233357

Author

Sattayapiwat, Olivia

Publication Date

2026-06-25

Peer reviewed|Thesis/dissertation

Benign Breast Disease and Breast Cancer Risk:
Implications for Risk Assessment and Clinical Interpretation

By

OLIVIA SATTAYAPIWAT
DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Epidemiology

in the

OFFICE OF GRADUATE STUDIES

of the

UNIVERSITY OF CALIFORNIA

DAVIS

Approved:

Diana Miglioretti, Chair

Theresa Keegan

Alexander Borowsky

Karla Kerlikowske

Committee in Charge

2026

Acknowledgements

My sincerest gratitude goes first and foremost to my mentor and dissertation chair, Dr. Diana Miglioretti. Thank you for giving me the opportunity to work with you on research that is both highly relevant and impactful. I am deeply grateful for your advice, support, and mentorship throughout every stage of my PhD. From encouraging me to apply for the F31 fellowship to preparing me for presentations, conferences, and future career opportunities, you consistently challenged me to grow while providing the support and guidance I needed along the way. Thank you for patiently helping me improve my writing, strengthen my research, and become a better scientist. It has been the greatest fortune of my education to work with and learn from you.

I would also like to thank Karla Kerlikowske, Theresa Keegan, Brian Sprague, Donald Weaver, and Sandy Borowsky for their mentorship, guidance, and support throughout my doctoral training. Your expertise and thoughtful feedback strengthened both this dissertation and my development as a researcher, and I am thankful for all that I have learned from each of you.

I would also like to thank the many colleagues and collaborators who supported this work. I am especially grateful to the current and past programmers at the Statistical Coordinating Center, including Kyung Won Lee, Joey Eavey, Laura Ichikawa, and Chi Tran, whose help and expertise made this research possible. I also thank Ellen O'Meara and Gaia Pocobelli for their support and coordination throughout my training. I would also like to thank the past and present members of the SABIR team, particularly Michael Bissell for generously sharing his programming expertise and answering my many questions, and

Yang Vang and Evan de Bie for their guidance and support during my early years in the program. Finally, thank you to Matt Ponzini for translating this work into a practical web-based application.

I would also like to acknowledge the support of the National Cancer Institute F31 Award, the Translational Health Data Science Fellowship, and the Ellen B. Gold Fellowship.

I would also like to thank my friends for their encouragement, companionship, and support. Special thanks to Zeyan for encouraging me to pursue a PhD and helping me find the confidence to pursue this path, and to Julia for her thoughtful feedback on my applications and for cheering me on along the way. I am thankful to Carol and Xiaohong for their friendship throughout graduate school and for the many memories we shared, from trips and sleepovers to late-night mahjong games. I would also like to thank Marilyn for her friendship and support throughout our time in the program, from conferences and seminars to the many ups and downs we navigated together. Finally, I would like to thank Jae, Maggie, Lena, Patrick, Phung, Ara, Mina, Willa, Tracy, Diana, Kathy, Linda, Lakmali, Iris, Tiffany, Maya, Jennie, Andrea, Chen, Donald, Eleanor, Erin, Lydia, and my cousins Anita and Felicia for their friendship and support over the years.

Finally, I would like to thank my parents, Woody and Annie, for their constant love and support. I am grateful for the sacrifices they made to provide me with the best education and opportunities possible, and for always encouraging me along the way. Thank you to my brother, Gabriel, for simply spending time with me through the years, whether trying new restaurants, watching TV shows, or playing Overcooked!.

BENIGN BREAST DISEASE AND BREAST CANCER RISK: IMPLICATIONS FOR RISK ASSESSMENT AND CLINICAL INTERPRETATION

Abstract

Background: Benign breast disease (BBD) is a common breast biopsy finding encompassing a diverse spectrum of diagnoses ranging from normal variations in breast tissue to proliferative changes with or without atypical features. Women with certain BBD diagnoses are known to have an increased risk of invasive breast cancer, with risk varying by histological degree of cancerous-like features within the benign lesion. However, risk estimates have primarily been quantified for established high-risk lesions, and risks associated with many other BBD diagnoses remain incompletely characterized.

Methods: This dissertation evaluates the association between specific BBD diagnoses and subsequent risk of invasive breast cancer and ductal carcinoma *in situ* in a large, population-based cohort from the Breast Cancer Surveillance Consortium. Using time-to-event and competing risk methods, we characterize heterogeneity in risk across individual diagnoses within conventional histologic categories and develop a harmonized classification framework to standardize BBD terminology. In addition, we examine laterality-specific patterns of breast cancer occurrence to provide insight into potential biological mechanisms underlying having a BBD diagnosis.

Results: Associations between BBD diagnoses and breast cancer varied substantially within commonly used histologic categories. We also observed that most associations between BBD diagnoses and breast cancer risk declined with increasing time since biopsy. We additionally developed a harmonized BBD classification framework and

companion web application to standardize BBD terminology and support consistent risk assessment. Laterality analyses demonstrated that BBD diagnoses were associated with bilateral breast cancer risk, with stronger ipsilateral than contralateral risk for both invasive breast cancer and DCIS, particularly within the first 10 years after biopsy.

Conclusion: Together, these findings provide precise estimates of breast cancer risk associated with BBD and demonstrate substantial heterogeneity within conventional histologic categories. This work supports improved breast cancer risk prediction, more individualized screening and prevention strategies, and standardized integration of BBD pathology data in research and clinical settings. The observed laterality-specific risk patterns may also provide insight into etiologic mechanisms underlying breast carcinogenesis.

Table of Contents

Introduction	1
Chapter 1: Advancing Evidence of the Associations between specific Benign Breast Diagnoses and Future Breast Cancer Risk	6
Abstract.....	7
Introduction	9
Methods	10
Results	14
Discussion.....	18
Chapter 2: Development of a Harmonized Classification Schema for Benign Breast Disease: A Multi-Registry Approach to Standardizing Diagnostic Terminology	55
Abstract.....	56
Introduction	58
Development.....	59
Approach.....	60
Discussion.....	64
Conclusion	67
Chapter 3: Ipsilateral and Contralateral Breast Cancer Risk Following Benign Breast Disease	72
Abstract.....	73
Introduction	75
Methods	76
Results	81
Discussion.....	83
Conclusion and Public Health Implications	94
REFERENCES	96

List of Tables

<i>Table 1.1.</i> Descriptive characteristics of study cohort (n=1,730,769 observations), 1994 to 2022..	25
<i>Table 1.2.</i> Individual BBD diagnoses and descriptors, sorted from most frequent to less frequent.....	27
<i>Table 1.3.</i> Hazards ratios (HR) and 95% confidence intervals for the association between benign breast disease diagnoses and subsequent invasive carcinoma or DCIS.....	29
<i>Table 1.4.</i> Hazards ratios (HR) and 95% confidence intervals for the association between benign breast disease diagnoses and subsequent invasive carcinoma or DCIS, by time since biopsy or mammogram.....	31
<i>Table S1.1.</i> Most common combinations of BBD diagnoses within the same biopsy episode among women with multiple BBD diagnoses.....	33
<i>Table S1.2.</i> Most common combinations of BBD diagnoses including columnar cell lesions within the same biopsy episode.....	37
<i>Table S1.3.</i> Most common combinations of BBD diagnoses including papillomatosis within the same biopsy episode.....	39
<i>Table S1.4.</i> Most common combinations of BBD diagnoses including atrophy within the same biopsy episode.....	41
<i>Table S1.5.</i> Most common combinations of BBD diagnoses including calcifications within the same biopsy episode.....	43
<i>Table S1.6.</i> Most common combinations of BBD diagnoses including sclerosing adenosis within the same biopsy episode.....	45
<i>Table S1.7.</i> Most common combinations of BBD diagnoses including apocrine metaplasia within the same biopsy episode.....	47
<i>Table S1.8.</i> Most common combinations of BBD diagnoses including adenosis within the same biopsy episode.....	49
<i>Table S1.9.</i> Hazards ratios (HR) and 95% confidence intervals for the association between benign breast disease diagnoses and subsequent invasive carcinoma.....	51
<i>Table S1.10.</i> Hazards ratios (HR) and 95% confidence intervals for the association between benign breast disease diagnoses and subsequent DCIS.....	53
 <i>Table 2.1.</i> Harmonized benign breast disease classification schema.....	 69
 <i>Table 3.1.</i> Descriptive characteristics of study cohort (n=1,726,999 observations), 1994 to 2022..	 88

<i>Table 3.2. Hazard Ratios for Invasive Carcinoma and Ductal Carcinoma In Situ by Broad Benign Breast Disease Category and Laterality.....</i>	<i>90</i>
<i>Table 3.3. Laterality-specific Hazard Ratios for Invasive Breast Carcinoma and Ductal Carcinoma In Situ by Specific Benign Breast Disease Diagnoses.....</i>	<i>91</i>

List of Figures

Figure 2.1. Development of the harmonized benign breast disease (BBD) classification.....68

Figure 2.2. Web-based application for mapping pathology terminology to standardized benign breast disease (BBD) diagnoses.....70

Figure 3.1. Laterality-specific breast cancer diagnoses by time since benign breast disease diagnosis, according to histologic category.....92

Figure 3.2. Laterality-specific breast cancer diagnoses by time since benign breast disease diagnosis, by cancer type.....93

Introduction

Benign breast disease and breast cancer risk

More than 1.6 million breast biopsies are performed annually among women in the United States, typically following abnormal breast imaging (1). Benign breast disease (BBD) is diagnosed in approximately 75% of these biopsies (2) and encompasses a broad spectrum of conditions, ranging from normal variations in breast tissue to proliferative lesions with or without atypia. While these findings are often considered benign, certain BBD diagnoses are associated with an increased risk of subsequent breast cancer, with risk varying by degree of proliferation and architectural atypia within the lesion (3, 4).

Because the histologic appearance of the benign lesion is a key determinant of breast cancer risk, BBD is commonly categorized into four histologic groups based on expert opinion of perceived future risk: non-proliferative lesions (lowest risk), proliferative changes without atypia, proliferative changes with atypia, and lobular carcinoma in situ (highest risk) (5-7). Women with atypical hyperplasia have an approximately 3.5–5.0-fold increased risk, whereas those with proliferative disease without atypia have an approximately 1.5–2.0-fold increased risk of invasive breast cancer, compared with women in the general population (4, 8, 9). However, findings on the association between non-proliferative lesions and subsequent breast cancer risk have been inconsistent (8, 10-13). A meta-analysis reported a null association, with summary relative risks ranging from 0.75 to 1.60 and evidence of potential publication bias (12), whereas a clinical trial observed a significantly increased risk among women with non-proliferative lesions or proliferative changes without atypia (13).

Evaluating associations between specific BBD diagnoses and future breast cancer may improve risk stratification and inform targeted screening and primary prevention. Current clinical breast cancer risk prediction models, including the BCSC v3 invasive cancer risk and BCSC advanced cancer risk models (14, 15), incorporate BBD history using these broad histologic categories (non-proliferative, proliferative without atypia, proliferative with atypia, and LCIS). However, the diversity of BBD diagnoses presents challenges for both research and clinical interpretation. Diagnostic terminology has evolved over time, and substantial inter-pathologist variability exists in the use and interpretation of pathologic terms, such that similar histologic findings may be described using different terminology and the same term may be applied inconsistently across settings. This lack of standardization complicates efforts to group similar type diagnoses, compare findings across studies, and accurately estimate risk associated with specific BBD entities.

Few studies have estimated the magnitude of breast cancer risk associated with other BBD diagnoses (13, 16-18), particularly within low-risk categories. One study examining these diagnoses was only able to detect an association for cysts (RR 1.6, 95% CI: 1.1–2.4) (13), while another study reported elevated risks for intraductal papilloma (RR 3.9, 95% CI: 2.0–7.4), adenosis (RR 2.5, 95% CI: 1.2–4.9), and fibrocystic diagnoses (RR 1.5, 95% CI: 1.1–1.9) (17). However, these studies were generally limited by modest sample sizes, resulting in wide confidence intervals and limited power to evaluate the full spectrum of BBD diagnoses.

There are additional limitations of existing evidence. Most available data are derived from excisional biopsies, and advances in imaging and image-guided core needle biopsy may influence the distribution and clinical implications of BBD diagnoses (3, 19, 20). Most risk prediction tools focus on invasive breast cancer, with relatively few evaluating risk for ductal carcinoma *in situ* (DCIS) (19), and many have been developed in populations with limited racial and ethnic diversity. Few studies of BBD and breast cancer risk have included women from racial or ethnic minority groups (13, 21-24), limiting generalizability. Given the complexity and diversity of BBD, it is important to discriminate and identify BBD diagnoses with increased underlying risk for breast cancer as well as diagnoses not associated with elevated risk to improve the accuracy of breast cancer risk prediction and clarify the biological and clinical significance of BBD diagnoses.

Laterality and disease processes

In addition to variation in overall risk, patterns of breast cancer occurrence following BBD may provide insight into the biological processes resulting in having a BBD diagnosis. A key question is whether BBD lesions act as direct precursors to cancer or instead reflect a broader tissue environment associated with increased susceptibility to cancer.

Laterality and timing of subsequent breast cancer may help distinguish between these possibilities (25). A high likelihood of cancers arising in the ipsilateral breast, particularly within a short interval following biopsy, would support a precursor role. In

contrast, persistent risk over time, including cancers occurring in the contralateral breast, would be more consistent with BBD acting as a marker of generalized susceptibility.

Despite this potential, relatively few studies have examined laterality patterns across a wide range of BBD diagnoses, and existing evidence has been largely limited to high-risk lesions in modestly sized cohorts (25-28). As a result, the relationship between BBD and subsequent breast cancer laterality remains incompletely understood.

Objectives and significance of the dissertation

The overall goal of this dissertation is to further characterize BBD by evaluating the risk of invasive breast cancer and DCIS associated with specific BBD diagnoses, developing a harmonized classification framework to standardize BBD terminology, and examining laterality patterns of subsequent breast cancer to provide insight into underlying disease processes.

Chapter 1 quantifies the risk of invasive breast cancer and DCIS associated with a comprehensive set of specific BBD diagnoses, evaluating heterogeneity in risk within and across conventional histologic categories. Chapter 2 describes the development of a harmonized classification framework for BBD diagnoses, integrating heterogeneous pathology terminology into standardized categories to support consistent risk assessment and clinical interpretation. Chapter 3 examines laterality-specific patterns of breast cancer following BBD, evaluating ipsilateral and contralateral risk over time to provide insight into potential biological mechanisms underlying disease progression.

Taken together, these studies provide updated and more precise estimates of breast cancer risk associated with BBD and improve understanding of disease heterogeneity. This work has the potential to improve risk prediction for women with a history of BBD, inform clinical management, and support more individualized screening and prevention strategies.

**Chapter 1: Advancing Evidence of the Associations between specific Benign Breast
Diagnoses and Future Breast Cancer Risk**

Olivia Sattayapiwat, Donald L. Weaver, Alexander D. Borowsky, Theresa H.M. Keegan,
Brian L. Sprague, Karla Kerlikowske, Diana L. Miglioretti

Abstract

Background: Benign breast disease (BBD) increases breast cancer risk; however, associations between specific BBD diagnoses and breast cancer risk are insufficiently studied.

Methods: Benign breast biopsies (N=131,724) from 1994–2022 were identified from eight Breast Cancer Surveillance Consortium registries. Pathological diagnoses were classified into 38 BBDs within 4 categories. For comparison, women with no prior breast biopsy and a negative screening mammogram (N=1,599,687) were identified. Associations of BBDs with invasive breast carcinoma and ductal carcinoma *in situ* (DCIS) were estimated using Fine-Gray competing risk models.

Results: Over a median follow-up of 7.5 years, 58,189 invasive breast cancers and 14,817 DCIS cases occurred. Lobular carcinoma *in situ* was associated with a 5.61-fold (95% confidence interval [CI]: 4.10–7.68) increased risk of invasive carcinoma and an 8.82-fold (95% CI: 5.39–14.4) increased risk of DCIS. Among proliferative changes with atypia BBDs, invasive cancer hazard ratios (HRs) ranged from 2.76–4.85; DCIS HRs, 5.07–8.51. Among proliferative changes without atypia BBDs, invasive HRs ranged from near-null (papillomatosis) to moderate and strong associations (e.g., HR=1.55 for usual ductal hyperplasia and 2.84 for multiple papillomas); DCIS HRs: 1.37–5.04. Nonproliferative BBDs were associated with low-to-moderate risk (invasive HRs: 0.63 for atrophy to 2.16 for benign breast parenchyma; DCIS HRs: 0.66–4.29). Most associations declined with increasing time since biopsy.

Conclusions: Associations between BBDs and breast cancer varied widely within commonly used histologic categories.

Impact: Advancing knowledge of specific BBD diagnoses may improve breast cancer risk prediction and support targeted screening and prevention strategies.

Introduction

A diagnosis of benign breast disease (BBD) is common throughout a woman's life, with a cumulative incidence of 10-20% (29-31) among women who present with lumps and/or undergo mammography. Overall prevalence of BBD estimated from autopsy studies is even higher, at approximately 50% (32). BBD encompasses a diverse spectrum of diagnoses, and varied diagnostic terms and classification systems have been applied over time and across pathologists (10, 33-35). Women with certain BBD diagnoses are known to have a higher risk for development of breast cancer (3, 4, 36).

BBD is often categorized into four histologic groups based on prior population-based studies and subsequent expert opinion of perceived future breast cancer risk: nonproliferative lesions (low risk) and proliferative changes without atypia, proliferative changes with atypia, and lobular carcinoma *in situ* (LCIS) (high risk) (5-7). Estimates of increased risk associated with specific BBD diagnoses have primarily been quantified for those within high risk categories, such as atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH) and LCIS (6, 27). More generally, studies have demonstrated that women in the atypical hyperplasia category have an approximately 3.5-5.0-fold increased risk, and women in the proliferative disease without atypia category are at an approximately 1.5-2.0-fold greater risk of future invasive breast cancer, compared with women in the general population (4, 8, 9). However, only a few studies have estimated the magnitude of breast cancer risk associated with other specific BBD diagnoses (13, 16-18).

Evaluating associations between specific BBD diagnoses and future breast cancer may improve risk stratification and inform targeted screening and primary prevention. These goals are complicated by the ongoing evolution of pathologic diagnostic terminology and by inter-pathologist variation and subjectivity in the use of diagnostic terms. To address these challenges, we used data from a large cohort of women undergoing mammography at facilities participating in the Breast Cancer Surveillance Consortium (BCSC; <https://www.bcsc-research.org>) to comprehensively characterize and update population-based associations of specific BBD diagnoses and subsequent invasive breast carcinoma and ductal carcinoma *in situ* (DCIS) risk.

Methods

Study Setting and Cohort

This study includes data from eight BCSC breast imaging registries: Carolina Mammography Registry in North Carolina; New Hampshire Mammography Network; Sacramento Area Breast Imaging Registry; San Francisco Mammography Registry; Northwest Screening and Cancer Outcomes Research Enterprise; Vermont Breast Cancer Surveillance System; Kaiser Permanente Washington Registry; and Metro Chicago Breast Cancer Registry. Registries submit data to a central Statistical Coordinating Center (SCC), which pools the data. Each BCSC registry and the SCC have received institutional review board approval for all study procedures, including informed consent, passive permission or a waiver of consent to enroll participants, link data, and perform analytic studies. All procedures are Health Insurance Portability and Accountability Act compliant. All registries

and the SCC have received a Federal Certificate of Confidentiality and other protections for the identities of women, physicians, and facilities who are subjects of this research.

Measures, Definitions, Outcomes

The following demographic characteristics and health history data were collected on patient intake forms at the time of breast imaging or from the electronic health record: height and weight; family history of breast cancer; date of last mammogram; history of breast cancer and breast procedures; and menopausal status. Health history data were linked with radiology, pathology, cancer registry, and state death data to capture the continuum of breast care using medical record numbers or matching algorithm software with strong identifiers. Breast cancer diagnoses before and after BCSC cohort entry were obtained from state or regional cancer registries.

For each breast biopsy, BBD diagnoses were manually abstracted by BCSC registry staff from pathology reports or entered in radiology management software by breast imaging technologists. Specific pathological terms were grouped into 38 BBD diagnoses, mapped in consultation with two expert breast pathologists (DW, AB). Diagnoses from multiple biopsies performed on the same day were combined into a single episode. The 38 BBD diagnoses were categorized into four histological categories: LCIS, proliferative changes with atypia, proliferative changes without atypia, and nonproliferative lesions that include both benign epithelial and stromal diagnoses. LCIS and proliferative changes with atypia were classified as high-risk histologic diagnoses, given their well-documented association with elevated future breast cancer risk (37-39), while proliferative changes without atypia and nonproliferative were classified as low-risk histologic diagnoses (16).

We excluded low-risk histologic findings for women with any high-risk histologic diagnosis. Women with both LCIS and proliferative changes with atypia were classified as LCIS. No hierarchical classification was applied within the low-risk categories, allowing for the inclusion of multiple low-risk histologic diagnoses.

Participants

We identified 159,544 benign breast biopsies performed during 1994–2022 in 137,183 women aged 35–79 years without any history of breast cancer. We excluded biopsies performed after the date each BCSC registry had complete cancer capture or within 6 months prior to that date (n=17,449); biopsies followed by a breast cancer diagnosis within 6 months (n=3,084) to remove prevalent cancers; and biopsies in women who died within 6 months of biopsy (n=149) or had a prior mastectomy (n=515). Further, we excluded biopsies if the last breast imaging exam recorded in the BCSC was more than 4.5 years prior (n=7,272). This resulted in 131,075 biopsy episodes among 112,856 women.

For comparison when estimating associations with breast cancer risk, we included all women (n=1,599,694) from the same registries with a negative screening mammography assessment (American College of Radiology BI-RADS 1 or 2) (40) with no breast cancer diagnosed within the following 6 months and without a prior breast biopsy, breast cancer diagnosis, or mastectomy. If multiple eligible mammograms were available for a woman, one was randomly selected. Women could also be in the comparison group if they had a negative mammogram prior to their first breast biopsy.

Statistical Approach

Analyses were performed using the single-day breast biopsy episode or mammogram (for women without a breast biopsy) as the unit of analysis. We summarized characteristics of the study population for biopsy episodes with high-risk histologic diagnoses, biopsy episodes with low-risk histologic diagnoses, and women with a negative screening mammogram. The prevalence of BBD diagnoses was characterized by calculating the percentage of biopsies associated with each respective BBD diagnosis. The percentage of biopsies with an additional, concurrent BBD diagnosis was also reported.

We estimated the hazard ratios (HRs) and 95% confidence intervals (95% CI) to measure the association between each BBD diagnosis and breast cancer risk using a partly conditional competing-risk regression model (41) based on the Fine-Gray approach (42). This approach allows women to enter the model multiple times, incorporating results from multiple breast biopsy episodes. For women with BBD, follow-up started 6 months after each biopsy to avoid including prevalent breast cancers. For women without a history of BBD (reference group), follow-up started 6 months after the screening mammogram date. Follow-up for each observation terminated at the earliest of a breast cancer diagnosis, death, end of complete cancer capture for the BCSC registry, 5 years after the last breast imaging in the BCSC, or 10 years for the main risk analysis. Separate models were fit for invasive breast carcinoma and DCIS. Death and diagnosis of cancer of other type (e.g., DCIS when modeling invasive carcinoma) were specified as competing events. A robust sandwich variance estimator and inverse-weighting by the number of observations were used to account for correlation among multiple biopsies from the same woman (43). BCSC

registry was included as a stratification variable. We fit one model with adjustment only for age and a second model further adjusted for concurrent BBD diagnoses. In a sensitivity analysis, we further adjusted for potential confounding factors, including race/ethnicity, family history of breast cancer, body mass index, menopausal status, and breast density.

To evaluate whether the association between BBD diagnoses and risk of breast cancer varied by time since diagnosis, separate models were fit to estimate the breast cancer HRs by time from biopsy, categorized as <5 years, 5-10 years, >10 years, extending the follow-up to the maximum observed time of 28 years. Heterogeneity by time period was assessed by refitting competing-risk regression models based on the Fine-Gray approach with time-varying indicators of the presence of BBD within the same intervals, and comparing interval-specific HRs using Wald tests from CONTRAST statements.

Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant.

Results

Over a median of 7.5 years (IQR=4.5-10 years) of follow-up, 35,251 invasive breast cancers and 9,743 DCIS were observed.

The age distribution was similar between the low-risk histology group and the negative mammogram group (**Table 1**), while high-risk histologic diagnoses tended to occur in older and post-menopausal women. Non-Hispanic White women had a higher

representation and Non-Hispanic Black women had lower representation in the high-risk histologic group compared with the low-risk histologic and negative mammogram groups. A family history of breast cancer or dense breasts (heterogeneously or extremely dense) were most common among the high-risk histologic group, less common in the low-risk group, and lowest among women in the negative mammogram group. Breast cancer was diagnosed more often among the high-risk histology group.

The five most common BBD diagnoses were fibroadenoma (23.9%), calcifications (21.6%), fibrocystic changes not otherwise specified (NOS) (18.6%), fibrosis (16.2%), and usual ductal hyperplasia (15.7%) (**Table 2**). Multiple diagnoses were observed for X% of biopsy episodes. The most common co-occurrence of BBD diagnoses was fibrocystic changes and calcifications (**Supplemental Table 1**). Columnar cell lesions, papillomatosis, atrophy, calcifications, sclerosing adenosis, apocrine metaplasia, and adenosis occurred >80% of the time with other BBD diagnoses (**Table 2**). Patterns of BBD co-occurrence are summarized in **Supplemental Tables 2–8**.

Adjusted HRs were strongest for LCIS: 5.61 (95% CI: 4.10–7.68) for invasive carcinoma and 8.82 (95% CI: 5.39–14.4) for DCIS, compared with women with negative screening mammograms (**Table 3**). Women with proliferative changes with atypia diagnoses had a HR of 4.10 (95% CI: 3.66–4.59) for invasive cancer and 6.18 (95% CI: 5.16–7.39) for DCIS. Women with proliferative changes without atypia diagnoses had a HR of 2.49 (95% CI: 2.32–2.67) for invasive cancer and 3.92 (95% CI: 3.49–4.39) for DCIS, which decreased to 1.51 (95% CI: 1.39–1.64) and 2.40 (95% CI: 2.08–2.76), respectively, after adjustment for co-occurring BBD. Women with nonproliferative lesions had an invasive

cancer HR of 2.08 (95% CI: 2.00–2.16) and DCIS HR of 2.27 (95% CI: 2.11–2.45) (**Table 3**), which decreased to 1.90 (95% CI: 1.82–1.99) and 1.86 (95% CI: 1.70–2.02), respectively, after adjustment for co-occurring BBD.

Adjusted HRs varied substantially across specific BBD diagnoses within the four broad groupings (**Table 3**). Among women with proliferative changes with atypia, invasive cancer HRs for specific BBD diagnoses ranged from 2.76 (95% CI: 0.92–8.29) for papillary with atypia to 4.85 (95% CI: 3.92–6.02) for ALH, while DCIS HRs ranged from 5.07 (95% CI: 3.40–7.55) for ALH to 8.51 (95% CI: 3.60–20.1) for atypical hyperplasia (mixed). For those with proliferative changes without atypia, invasive cancer risk varied widely, ranging from near-null and non-significant associations (e.g., HR=1.06 for papillomatosis, HR=1.24 for radial scar, and HR = 1.22 for columnar cell lesions) to moderate risk (e.g., HR=1.55 for usual ductal hyperplasia) and strong associations (e.g., HR=2.84 for multiple papillomas). DCIS associations within this category were generally of greater magnitude, with HRs ranging from 1.37 for papillomatosis to 5.04 for multiple papillomas. Among nonproliferative BBDs, invasive cancer HRs ranged from 0.63 for atrophy to 2.16 for benign breast parenchyma, while DCIS HRs ranged from 0.66 for fibroadenomatoid change/hyperplasia to 4.29 for phyllodes tumor. While many nonproliferative diagnoses showed no significant association with either outcome, modest but statistically significant associations were observed for several commonly diagnosed entities, including fibroadenoma, calcifications, and fibrocystic changes NOS. Within the proliferative changes without atypia and nonproliferative categories, HRs for many diagnoses, such as columnar cell lesions and radial scars (proliferative without atypia) and

pseudoangiomatous stromal hyperplasia or apocrine metaplasia (nonproliferative), attenuated after adjustment for co-occurring BBD.

When the analysis was further adjusted by race and ethnicity, breast density, menopausal status, body mass index, and family history, the overall associations between BBD diagnoses and breast cancer risk remained generally consistent, with modest attenuation of most HRs (**Supplemental Tables 9-10**).

Table 4 shows HRs by time since BBD diagnosis. When follow-up was extended to 28 years, 22,938 invasive breast cancers and 5,074 DCIS were observed. LCIS conferred the highest risk for both invasive cancer and DCIS across all time intervals with the risk for invasive cancer declining after 10 years and the risk for DCIS declining after 5 years, although these declines were not statistically significant.

Risk for invasive cancer declined significantly over time among women with proliferative lesions with atypia from 4.55 (95% CI: 3.95–5.25) within 5 years to 3.62 (95% CI: 3.01–4.34) and 2.64 (95% CI: 2.11–3.29) at later intervals ($p < 0.05$ for difference compared to < 5 years). Nonproliferative lesions also showed a statistically significant decline in risk over time (HRs = 2.05, 1.76, 1.37 at < 5 , 5-10, and > 10 years). HRs for proliferative lesions without atypia exhibited smaller, non-significant declines across follow-up. A similar temporal pattern was observed for risk of DCIS, with significant declines in risk over time among women with proliferative lesions with atypia and nonproliferative lesions. HRs for proliferative lesions without atypia showed a gradual decline, with the reduction reaching statistical significance only after 10 years (HR = 1.89,

95% CI: 1.49–2.39) compared with within 5 years (HR: 2.50, 95% CI = 2.08–3.00).

Significant declines in risk over time were also observed for selected individual diagnoses within these categories (**Table 4**).

Discussion

In this large cohort study of BBD, we found that the magnitude of elevated risk of invasive breast carcinoma and DCIS following BBD diagnosis varied substantially between broad histologic categories and among specific BBD diagnoses within these broad categories. We found LCIS and proliferative BBD showed stronger associations with DCIS than invasive cancer, whereas nonproliferative BBD tended to exhibit low overall risk for DCIS and invasive carcinoma with similar risk for each. The BBD diagnoses most strongly associated with invasive cancer (HR>3.5) included LCIS, ALH, ADH, atypical hyperplasia mixed, and atypical hyperplasia NOS. BBD diagnoses strongly associated with DCIS included LCIS, all diagnoses under the proliferative with atypia category, multiple papillomas, and phyllodes tumor. Most associations between BBD diagnoses and breast cancer risk declined with increasing time since biopsy. Together, these findings provide updated knowledge of the relationship between BBD and breast cancer risk with improved precision and the potential to directly impact clinical practice.

Our findings have implications for breast cancer risk prediction models. Current clinical models, including the BCSC v3 invasive cancer risk and BCSC advanced cancer risk models (14, 15) incorporate BBD history using broad categories (nonproliferative,

proliferative without atypia, proliferative with atypia, and LCIS). However, our results demonstrate substantial heterogeneity among specific BBD diagnoses within these categories. For example, within proliferative without atypia lesions, multiple papillomas were consistently associated with elevated breast cancer risk, while usual ductal hyperplasia carried only moderate risk. Incorporating these specific BBD diagnoses into risk models may improve individual-level risk stratification and help providers identify women most likely to benefit from enhanced preventive strategies. For example, radial scar had an HR for invasive carcinoma of 1.24, which is lower than the 1.70 assigned in BCSC v3 model (14) for biopsies with proliferative without atypia, suggesting that specifying this diagnosis would slightly reduce predicted risk. In contrast, multiple papillomas, with an HR of 2.84, well above 1.70, would substantially increase estimated risk. Future work should explore whether integrating these specific BBD diagnoses into clinical risk prediction tools could refine absolute risk estimates.

Notably, by allowing both proliferative changes without atypia and nonproliferative lesions to co-exist with the same biopsy episode, we observed that adjustment for co-occurring BBD decreased the HRs for invasive cancer. This attenuation reflects the shared contribution of overlapping diagnoses within the model and should not be interpreted as indicating lower overall risk, as women with multiple diagnoses may have higher combined risk than those with a single diagnosis. In prior studies, such co-existing diagnoses were typically handled by assigning each biopsy to the highest-risk category in a hierarchical structure (e.g., atypical hyperplasia > proliferative without atypia > nonproliferative) (4, 44, 45). In contrast, because of our non-hierarchical approach, overlapping histologic features

could be represented across categories, which may reduce differences in estimated risk between proliferative and nonproliferative groups. These findings highlight the extent to which shared or overlapping pathology contributes to observed risk patterns across categories. In addition, the breast biopsy may not always identify the highest risk benign disease within the breast. This sampling bias can be attributed to both radiology (imprecise targeting) and pathology (imprecise tissue sampling).

Prior studies have similarly demonstrated the magnitude of breast cancer risk associated with commonly diagnosed BBD. A previous study in the New Mexico Mammography Project found 2-4-fold greater risk for breast cancer in women with several BBD diagnoses, such as adenosis, apocrine metaplasia, calcifications, and usual ductal hyperplasia (16). In an analysis within the Breast Cancer Prevention Trial, specific BBD diagnoses within lower risk categories were also explicitly investigated, but the study only had sufficient power to find a significant association between cysts and breast cancer (13). Other studies have focused on selected benign breast lesions, such as sclerosing adenosis, radial scars, complex fibroadenomas, and flat epithelial atypia (21-24). However, these studies had modest sample sizes for each diagnosis, leading to wide confidence intervals and insufficient power to fully assess the wide spectrum of BBD diagnoses. Additionally, the great majority of these prior studies used data derived from excisional biopsies, and it is likely that improvements in imaging and image-guided core needle biopsy could result in different distributions of BBD diagnoses with different risk implications (3, 19, 20). Moreover, while a limited number of risk prediction models have considered DCIS as an outcome (19, 46), most studies of BBD and breast cancer risk have

either treated DCIS as a competing risk in their analysis or examined breast cancer risk overall (invasive breast cancer combined with DCIS). To our knowledge, few studies have specifically evaluated BBD in relation to risk of DCIS as a distinct endpoint.

LCIS has historically been variably classified as either a benign lesion or an *in situ* carcinoma and was not uniformly included in earlier BBD studies. In this analysis, LCIS was included in accordance with its classification in contemporary breast cancer risk assessment frameworks. The strong associations observed between LCIS and proliferative lesions with atypia and subsequent DCIS may partly reflect the intensive monitoring these women typically undergo, which could lead to earlier detection of non-invasive disease. However, surveillance alone is unlikely to fully explain the elevated risks observed in our study. Substantial heterogeneity in risk across specific proliferative lesions with atypia suggests that certain BBD diagnoses may reflect distinct underlying etiologic pathways that increase susceptibility to breast cancer. These findings provide insight into potential biological mechanisms through which BBD may influence the development of both invasive and non-invasive breast cancer.

Notably, the magnitude of invasive breast cancer risk associated with proliferative lesions with atypia in our study is comparable to estimates reported following DCIS in population-based studies (47, 48). For example, in an analysis of the California Cancer Registry (48), women diagnosed and treated for DCIS experienced elevated risks of subsequent invasive breast cancer relative to the general population, with standardized incidence ratios ranging from approximately 1.4 to 1.7 depending on laterality. In contrast, a Norwegian population-based registry study reported a substantially higher relative risk

following DCIS (SIR $\approx$ 5) (47). Differences in reported risk estimates across studies likely reflect variation in outcome definitions, laterality-specific analyses, and analytic framing rather than fundamental differences in underlying biology. Viewed in this context, the magnitude of risk associated with proliferative lesions with atypia in our study falls within the range of risk estimates reported following DCIS in population-based settings and represents a clinically meaningful level of risk.

Our findings examining time since biopsy suggest that risk following high-risk histologic diagnoses, particularly LCIS and proliferative changes with atypia BBD, is most pronounced in the first 5 years after biopsy, with a general downward trend over time. Proliferative changes with atypia BBD and nonproliferative BBD both demonstrated statistically significant declines in HR over time, although risk estimates among nonproliferative diagnoses remained substantially lower than that for high-risk lesions. The observed decline in risk over time among nonproliferative BBD diagnoses may also reflect, in part, differential follow-up or surveillance patterns, such as a lower likelihood of subsequent biopsies compared with women with higher-risk lesions. Our findings on temporal changes in risk are broadly consistent with prior cohorts (6, 17, 45, 49) and provide greater resolution due to the length of follow-up in the BCSC. On the other hand, one cohort observed an increasing risk persisting for at least 15 years among women with proliferative disease, with or without atypia (50). These discrepancies likely reflect differences in study design, population characteristics, and analytic approaches, including variation in follow-up duration, age-related changes in baseline breast cancer risk, hormonal exposures over time, and how BBD categories are defined. The observed

temporal variation across BBD categories has important implications for long-term surveillance and chemoprevention strategies.

The strong association we found between phyllodes tumor and subsequent DCIS warrants further investigation. Although speculative, this relationship may reflect intrinsic stromal–epithelial interactions characteristic of phyllodes lesions. Perhaps some of the same host factors, especially mitogenic stimuli, promote both phyllodes tumor and DCIS. We also noted that calcifications remained associated with subsequent breast cancer even after adjustment for co-occurring BBD diagnoses. Because calcifications can arise within a wide range of underlying breast abnormalities (51), future studies should evaluate whether specific calcification patterns or pathological contexts modify the relationship between BBD diagnoses and subsequent cancer risk.

To our knowledge, this is the largest study to date evaluating the association between specific BBD diagnoses and subsequent risk of invasive breast cancer and DCIS. Our study includes more than 73,000 incident breast cancer cases with up to 28 years of follow-up in a racial and ethnically diverse population. We included multiple biopsies for a woman. While 6.1% of women had multiple biopsies within 6 months, only 2.3% of women had diagnoses that were in different histologic categories. Potential reverse causation was minimized because women with cancer diagnosed within 6 months of biopsy were excluded from our study. Using data reported from pathologists from multiple sites without having biopsy material for central review may result in misclassification but reflects real world clinical practice. Estimating breast cancer risk based on the diagnoses of practicing

pathologists provides risk values that relate directly to the actual pathologic diagnoses that are used as the basis for decision-making in clinical practice.

In conclusion, our extensive analysis using data from the BCSC cohort provides additional knowledge about the association between specific BBD diagnoses and subsequent breast cancer risk. Given the high prevalence of BBD in women, it is critical to precisely estimate future breast cancer risk for use in both clinical and research settings. These findings also inform more personalized screening and prevention strategies for women with a history of BBD, with the potential to reduce unnecessary breast imaging after a BBD diagnosis by targeting more intensive strategies to those at higher risk of breast cancer who may benefit the most.

Table 1.1 Descriptive characteristics of study cohort (n=1,730,769 observations), 1994 to 2022

Characteristic	Biopsies with high-risk histologic diagnoses, n=8,293(%)	Biopsies with low-risk histologic diagnoses, n=122,782 (%)	Negative mammograms, n=1,599,694 (%)
Age, years			
35-49	31.6	44.1	47.4
50-59	36.2	29.4	26.9
60-69	21.2	17.5	16.8
70-79	11.0	8.9	8.9
Race/ethnicity			
Asian / Pacific Islander	8.6	7.9	8.1
Black, non-Hispanic	9.8	12.8	13.3
Hispanic	4.8	5.3	5.4
White, non-Hispanic	74.6	71.8	71.1
Other / multiracial	2.1	2.2	2.1
Unknown	4.8	5.6	9.0
Postmenopausal			
No	46.4	54.5	53.1
Yes	53.6	45.5	46.9
1 st degree family history of breast cancer			
No	79.1	82.5	88.0
Yes	20.9	17.5	12.0
Unknown	11.2	12.8	20.6
BI-RADS breast density			
Almost entirely fat	3.6	4.9	8.4
Scattered fibroglandular densities	32.2	34.9	43.3
Heterogenously dense	51.4	47.5	39.4
Extremely dense	12.8	12.8	8.9
Unknown	6.4	7.4	4.8
Body mass index, kg/m ²			
Underweight (<18.5)	1.5	1.8	1.6
Normal (18.5 - 24.9)	41.3	40.2	40.5
Overweight (25.0-29.9)	28.4	27.3	28.5
Obese (≥30)	28.8	30.7	29.3
Unknown	41.1	41.9	49.9
Follow-up time (median) ^a years	6.1 (4.0—9.8)	6.5 (4.2—10.0)	7.6 (4.5—10.0)
Reason for end of follow-up			
Breast cancer diagnosis	10.6	4.8	2.4
Death	2.4	2.4	2.4
End of complete cancer capture	37.5	38.1	24.6

5 years after the last breast imaging in the BCSC	25.5	26.3	34.0
10 years	24.0	28.4	36.6

Percentage is among non-missing except for unknown row.

^aValues are expressed as median (interquartile range [IQR])

Table 1.2 Individual BBD diagnoses and descriptors, sorted from most frequent to less frequent

		Count	Percentage of biopsies with that diagnosis	Percentage of biopsies with an additional, concurrent diagnosis
BBD Group	BBD Diagnoses			
NPC	Fibroadenoma	31,374	23.9%	34.3%
NPC	Calcification	28,316	21.6%	87.0%
NPC	Fibrocystic changes NOS	24,396	18.6%	31.9%
NPC	Fibrosis	21,270	16.2%	72.3%
PWoA	Usual ductal hyperplasia	20,606	15.7%	79.9%
NPC	Cyst	11,658	8.9%	76.9%
NPC	Apocrine Metaplasia	9,637	7.4%	85.2%
NPC	Inflammation	8,261	6.3%	65.3%
NPC	Benign NOS	7,005	5.3%	1.3%
NPC	Adenosis	6,377	4.9%	82.6%
PWoA	Solitary Papilloma	6,199	4.7%	64.6%
NPC	Sclerosing adenosis	5,499	4.2%	85.6%
PWA	Atypical ductal hyperplasia	3,932	3.0%	0.5%
NPC	Benign breast parenchyma	3,647	2.8%	2.8%
PWoA	Columnar cell lesions	2,703	2.1%	95.6%
NPC	Pseudoangiomatous stromal hyperplasia	2,095	1.6%	69.4%
PWA	Atypical lobular hyperplasia	1,752	1.3%	0.1%
PWoA	Radial scar	1,514	1.2%	71.1%
NPC	Epithelial benign	1,369	1.0%	51.3%
NPC	Fibroadenomatous change/hyperplasia	1,339	1.0%	64.6%
PWA	Atypical hyperplasia NOS	936	0.7%	0.0%
NPC	Benign stromal neoplasm	764	0.6%	22.9%
LCIS	Lobular Carcinoma <i>in situ</i>	749	0.6%	0.0%
PWoA	Papillomatosis	643	0.5%	93.5%
NPC	Stromal benign	626	0.5%	37.5%
PWA	Atypia NOS	561	0.4%	1.1%
NPC	Phyllodes	552	0.4%	31.9%
NPC	Atrophy	321	0.2%	87.5%
PWoA	Multiple papillomas	311	0.2%	34.4%
PWoA	Flat Epithelial Atypia	289	0.2%	57.8%
PWA	Atypical hyperplasia mixed	272	0.2%	0.7%
NPC	Hemangioma	228	0.2%	20.6%
NPC	Adenoma	193	0.1%	59.1%
NPC	Skin	125	0.1%	1.6%
PWA	Papillary with atypia	121	0.1%	24.0%
NPC	Hamartoma	104	0.1%	43.3%
NPC	Adenomyoepithelioma	44	0.0%	47.7%

NPC	Squamous Metaplasia	29	0.0%	75.9%
-----	---------------------	----	------	-------

Abbreviations: BBD, benign breast disease; NOS, not otherwise specified; LCIS, lobular carcinoma *in situ*; PWA, proliferative changes with atypia; PWoA, proliferative changes without atypia; NPC, non-proliferative changes

Table 1.3. Hazards ratios (HR) and 95% confidence intervals for the association between benign breast disease diagnoses and subsequent invasive carcinoma or DCIS.

			Invasive breast cancer			DCIS	
	BBD No.	Case No.	HR (95% CI)*	HR ^a , adjusted for other BBD diagnoses	Case No.	HR (95% CI)*	HR ^a , adjusted for other BBD diagnoses
Negative mammogram		30,185	Referent [^]	Referent [^]	8,069	Referent [^]	Referent [^]
Lobular Carcinoma <i>in situ</i>	749	77	5.66 (4.28, 7.48)	5.61 (4.10, 7.68)	29	8.41 (5.37, 13.2)	8.82 (5.39, 14.4)
Proliferative changes with Atypia	7,544	544	4.09 (3.69, 4.54)	4.10 (3.66, 4.59)	231	6.17 (5.23, 7.27)	6.18 (5.16, 7.39)
Atypical lobular hyperplasia	1,752	139	4.91 (4.04, 5.97)	4.85 (3.92, 6.02)	41	5.75 (4.09, 8.10)	5.07 (3.40, 7.55)
Atypical ductal hyperplasia	3,932	288	3.92 (3.40, 4.52)	3.91 (3.33, 4.58)	136	6.28 (5.05, 7.80)	6.41 (5.04, 8.16)
Atypical hyperplasia mixed	272	17	3.76 (2.12, 6.65)	3.79 (1.97, 7.30)	12	9.25 (4.55, 18.8)	8.51 (3.60, 20.1)
Atypical hyperplasia NOS	936	71	3.79 (2.82, 5.08)	3.74 (2.74, 5.11)	25	5.92 (3.62, 9.71)	6.20 (3.72, 10.3)
Atypia NOS	561	25	2.98 (1.86, 4.76)	3.17 (1.91, 5.27)	14	6.51 (3.70, 11.5)	5.14 (2.55, 10.4)
Papillary with atypia	121	9	4.80 (1.87, 12.3)	2.76 (0.92, 8.29)	4	17.79 (6.16, 51.3)	5.53 (1.21, 25.2)
Proliferative changes without Atypia	27,809	1,176	2.49 (2.32, 2.67)	1.51 (1.39, 1.64)	474	3.92 (3.49, 4.39)	2.40 (2.08, 2.76)
Multiple papillomas	311	18	3.74 (2.20, 6.36)	2.84 (1.60, 5.05)	12	9.74 (5.13, 18.5)	5.04 (2.31, 11.0)
Solitary Papilloma	6,199	298	2.81 (2.46, 3.22)	1.68 (1.44, 1.95)	168	5.92 (4.91, 7.14)	3.29 (2.61, 4.16)
Flat Epithelial Atypia	289	10	2.49 (1.18, 5.28)	1.63 (0.69, 3.87)	6	5.96 (2.37, 15.0)	3.06 (1.00, 9.41)
Usual ductal hyperplasia	20,606	890	2.42 (2.23, 2.62)	1.55 (1.39, 1.72)	293	3.25 (2.83, 3.74)	1.73 (1.42, 2.12)
Radial scar	1,514	51	2.43 (1.75, 3.37)	1.24 (0.85, 1.81)	30	4.44 (2.80, 7.05)	1.54 (0.87, 2.72)
Columnar cell lesions	2,703	67	2.86 (2.13, 3.84)	1.22 (0.87, 1.70)	29	4.90 (3.16, 7.60)	1.51 (0.88, 2.59)
Papillomatosis	643	27	2.25 (1.45, 3.47)	1.06 (0.66, 1.70)	9	3.78 (1.89, 7.56)	1.37 (0.64, 2.93)
Nonproliferative Lesions	114,760	4,089	2.08 (2.00, 2.16)	1.90 (1.82, 1.99)	1,242	2.27 (2.11, 2.45)	1.86 (1.70, 2.02)
Benign breast parenchyma	3,647	119	2.11 (1.72, 2.60)	2.16 (1.74, 2.68)	30	1.87 (1.22, 2.88)	1.84 (1.17, 2.89)
Fibrocystic changes NOS	24,396	1,038	2.22 (2.06, 2.39)	1.94 (1.79, 2.10)	287	2.19 (1.91, 2.51)	1.79 (1.54, 2.09)
Benign NOS	7,005	233	1.94 (1.67, 2.26)	1.89 (1.62, 2.21)	88	2.90 (2.28, 3.69)	2.66 (2.06, 3.45)
Adenoma	193	8	2.76 (1.33, 5.69)	1.87 (0.86, 4.07)	1	0.70 (0.04, 11.3)	0.42 (0.03, 6.77)
Adenosis	6,377	306	2.78 (2.45, 3.16)	1.64 (1.41, 1.91)	86	2.79 (2.18, 3.56)	1.30 (0.97, 1.75)
Benign stromal neoplasm	764	28	2.12 (1.41, 3.19)	1.62 (1.03, 2.55)	8	2.04 (0.92, 4.52)	1.75 (0.78, 3.92)

Pseudoangiomatous stromal hyperplasia	2,095	51	2.29 (1.65, 3.17)	1.42 (1.00, 2.02)	13	2.10 (1.13, 3.90)	1.18 (0.60, 2.34)
Squamous Metaplasia	29	1	2.02 (0.30, 13.68)	1.39 (0.19, 10.5)	1	4.21 (0.26, 68.93)	2.65 (0.16, 45.0)
Fibroadenoma	31,374	903	1.81 (1.68, 1.95)	1.39 (1.28, 1.51)	269	1.89 (1.64, 2.17)	1.39 (1.19, 1.61)
Adenomyoepithelioma	44	2	3.08 (0.67, 14.3)	1.38 (0.22, 8.82)	0	N/A	N/A
Calcification	28,316	1,248	2.31 (2.15, 2.47)	1.35 (1.23, 1.48)	364	2.80 (2.46, 3.18)	1.48 (1.25, 1.76)
Phyllodes	552	14	1.58 (0.83, 2.99)	1.34 (0.64, 2.79)	10	4.88 (2.42, 9.85)	4.29 (1.96, 9.39)
Fibrosis	21,270	722	2.03 (1.86, 2.21)	1.31 (1.17, 1.46)	209	2.31 (1.97, 2.72)	1.17 (0.94, 1.45)
Epithelial benign	1,369	58	2.03 (1.51, 2.74)	1.30 (0.94, 1.78)	16	2.42 (1.38, 4.24)	1.46 (0.80, 2.65)
Sclerosing adenosis	5,499	201	2.28 (1.94, 2.68)	1.15 (0.96, 1.39)	87	3.28 (2.53, 4.25)	1.34 (0.98, 1.83)
Hamartoma	104	2	1.17 (0.24, 5.77)	1.13 (0.23, 5.58)	1	2.70 (0.39, 18.8)	2.57 (0.36, 18.3)
Cyst	11,658	404	1.96 (1.74, 2.20)	1.12 (0.97, 1.30)	132	2.60 (2.14, 3.16)	1.28 (0.99, 1.66)
Inflammation	8,261	238	1.68 (1.44, 1.95)	1.09 (0.92, 1.29)	69	1.89 (1.43, 2.51)	0.99 (0.72, 1.38)
Skin	125	3	1.03 (0.21, 5.12)	1.07 (0.21, 5.31)	3	6.22 (1.81, 21.4)	6.37 (1.86, 21.8)
Apocrine Metaplasia	9,637	315	1.92 (1.68, 2.18)	0.94 (0.80, 1.10)	102	2.38 (1.89, 2.99)	0.89 (0.67, 1.19)
Stromal benign	626	13	1.11 (0.57, 2.14)	0.89 (0.44, 1.80)	2	1.02 (0.26, 4.08)	0.86 (0.21, 3.51)
Fibroadenomatous change/hyperplasia	1,339	27	1.48 (0.95, 2.31)	0.88 (0.54, 1.41)	7	1.36 (0.56, 3.35)	0.66 (0.23, 1.84)
Hemangioma	228	5	1.00 (0.32, 3.11)	0.74 (0.20, 2.68)	1	1.31 (0.19, 9.23)	1.20 (0.17, 8.56)
Atrophy	321	10	1.01 (0.48, 2.13)	0.63 (0.28, 1.40)	1	0.35 (0.02, 5.55)	0.24 (0.01, 3.87)

Abbreviations: BBD, benign breast disease; CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified

*HRs (95% CI) are adjusted for age (continuous)

^aHRs for specific diagnoses are adjusted for concurrent diagnoses seen in this list

[^]Women with negative/benign mammograms are the reference group in all models

Table 1.4. Hazards ratios (HR) and 95% confidence intervals for the association between benign breast disease diagnoses and subsequent invasive carcinoma or DCIS, by time since biopsy or mammogram.

Invasive Hazard Ratio ^a (95% CI)						DCIS HR ^a (95% CI)						
	Case No.	<5 years	Case No.	5-10 years	Case No.	>10 years	Case No.	<5 years	Case No.	5-10 years	Case No.	>10 years
Negative mammogram	15,396	Referent ^a	14,789	Referent ^a	21,167	Referent ^a	4,142	Referent ^a	3,927	Referent ^a	4,674	Referent ^a
Lobular Carcinoma <i>in situ</i>	44	5.61 (3.70, 8.50)	33	6.18 (3.89, 9.82)	26	3.75 (2.24, 6.26)	21	11.2 (6.30, 19.9)	8	6.19 (2.45, 15.62)	0	N/A
Proliferative with Atypia	341	4.55 (3.95, 5.25)	203	3.62 (3.01, 4.34)^b	154	2.64 (2.11, 3.29)^b	166	7.72 (6.24, 9.54)	65	4.48 (3.25, 6.18)^b	37	3.10 (2.07, 4.65)^b
Atypical lobular hyperplasia	93	5.75 (4.42, 7.47)	46	3.83 (2.68, 5.48)	42	3.40 (2.31, 5.00) ^b	26	5.46 (3.27, 9.10)	15	4.93 (2.66, 9.12)	11	3.53 (1.64, 7.60)
Atypical ductal hyperplasia	183	4.49 (3.69, 5.46)	105	3.28 (2.53, 4.26) ^b	69	2.11 (1.49, 2.98) ^b	105	8.34 (6.32, 11.0)	31	3.87 (2.41, 6.22) ^b	14	2.54 (1.37, 4.71) ^b
Atypical hyperplasia mixed	13	4.85 (2.29, 10.3)	4	2.22 (0.59, 8.36)	11	5.30 (2.01, 14.0)	9	10.7 (3.96, 28.7)	3	7.48 (1.75, 32.0)	1	1.03 (0.03, 35.9)
Atypical hyperplasia NOS	30	2.90 (1.80, 4.67)	41	4.93 (3.26, 7.44)	30	2.58 (1.62, 4.13)	18	9.24 (5.19, 16.5)	7	3.07 (1.08, 8.76)	11	4.54 (2.15, 9.59)
Atypia NOS	18	3.28 (1.76, 6.13)	7	3.00 (1.27, 7.12)	2	4.23 (0.75, 24.0)	6	4.28 (1.66, 11.0)	8	8.81 (3.50, 22.2)	0	N/A
Papillary with atypia	6	2.62 (0.68, 10.1)	3	3.13 (0.49, 20.2)	2	18.2 (4.57, 72.5)	3	6.56 (1.33, 32.3)	1	3.19 (0.06, 176.4)	0	N/A
Proliferative without Atypia	699	1.50 (1.35, 1.68)	477	1.51 (1.34, 1.71)	472	1.48 (1.31, 1.68)	299	2.50 (2.08, 3.00)	175	2.28 (1.83, 2.84)	120	1.89 (1.49, 2.39)^b
Multiple papillomas	12	2.58 (1.23, 5.39)	6	3.39 (1.37, 8.36)	1	1.42 (0.18, 11.3)	9	5.78 (2.45, 13.7)	3	3.14 (0.53, 18.67)	1	6.78 (1.04, 44.1)
Solitary Papilloma	173	1.69 (1.38, 2.07)	125	1.70 (1.35, 2.14)	106	1.44 (1.10, 1.89)	107	3.56 (2.66, 4.77)	61	3.05 (2.10, 4.42)	28	1.92 (1.20, 3.08) ^b
Flat Epithelial Atypia	10	2.77 (1.17, 6.55)	0	N/A	5	1.51 (0.54, 4.22)	4	3.02 (0.73, 12.4)	2	3.04 (0.47, 19.6)	0	N/A
Usual ductal hyperplasia	520	1.53 (1.33, 1.77)	370	1.55 (1.33, 1.81)	385	1.44 (1.25, 1.67)	176	1.69 (1.30, 2.21)	117	1.85 (1.37, 2.48)	93	1.80 (1.36, 2.38)
Radial scar	30	1.09 (0.67, 1.80)	21	1.63 (0.94, 2.84)	10	0.98 (0.41, 2.33)	19	1.48 (0.74, 2.96)	11	1.49 (0.54, 4.05)	5	1.92 (0.52, 7.10)
Columnar cell lesions	50	1.03 (0.69, 1.52)	17	1.99 (1.03, 3.88)	3	2.84 (0.56, 14.5)	22	1.20 (0.63, 2.26)	7	2.80 (0.95, 8.24)	0	N/A
Papillomatosis	17	1.34 (0.75, 2.40)	10	0.78 (0.35, 1.70)	14	0.66 (0.34, 1.29)	5	1.17 (0.41, 3.39)	4	1.75 (0.59, 5.22)	9	2.23 (0.79, 6.30)
Nonproliferative Lesions	2,403	2.05 (1.93, 2.17)	1,686	1.76 (1.65, 1.89)^b	1,470	1.37 (1.28, 1.47)^b	773	2.08 (1.86, 2.33)	469	1.64 (1.44, 1.87)^b	335	1.32 (1.14, 1.52)^b
Benign breast parenchyma	83	2.59 (2.00, 3.36)	36	1.62 (1.11, 2.37) ^b	40	1.35 (0.93, 1.97) ^b	17	1.67 (0.89, 3.12)	13	2.07 (1.07, 4.01)	5	0.67 (0.21, 2.08)

Fibrocystic changes												
NOS	575	2.07 (1.86, 2.31)	463	1.81 (1.61, 2.04)	393	1.21 (1.06, 1.38) ^b	171	1.96 (1.61, 2.40)	116	1.64 (1.30, 2.08)	96	1.53 (1.19, 1.97)
Benign NOS	155	2.26 (1.86, 2.73)	78	1.50 (1.15, 1.95) ^b	59	1.33 (0.99, 1.77) ^b	67	3.70 (2.75, 4.97)	21	1.57 (0.95, 2.58) ^b	14	0.92 (0.46, 1.85) ^b
Adenoma	4	1.73 (0.59, 5.03)	4	1.99 (0.64, 6.18)	3	1.33 (0.38, 4.69)	1	0.74 (0.05, 12.0)	0	N/A	1	1.86 (0.23, 15.1)
Adenosis	167	1.59 (1.30, 1.95)	139	1.68 (1.35, 2.10)	117	1.32 (1.02, 1.71)	58	1.53 (1.06, 2.20)	28	1.09 (0.67, 1.77)	32	1.52 (0.90, 2.58)
Benign stromal neoplasm	14	1.26 (0.62, 2.53)	14	2.05 (1.13, 3.70)	10	1.07 (0.51, 2.24)	3	1.09 (0.27, 4.38)	5	2.64 (0.99, 7.05)	3	1.23 (0.28, 5.38)
Pseudoangiomatous stromal hyperplasia	40	1.61 (1.09, 2.39)	11	1.02 (0.47, 2.21)	3	1.92 (0.72, 5.16)	8	0.88 (0.36, 2.15)	5	2.08 (0.72, 6.02)	2	3.58 (0.53, 24.2)
Squamous Metaplasia	1	2.76 (0.37, 20.4)	0	N/A	2	1.80 (0.36, 8.97)	1	5.06 (0.29, 86.8)	0	N/A	0	N/A
Fibroadenoma	511	1.40 (1.25, 1.56)	392	1.41 (1.25, 1.59)	404	1.33 (1.18, 1.50)	149	1.36 (1.11, 1.66)	120	1.47 (1.17, 1.83)	94	1.29 (1.00, 1.65)
Adenomyoepithelioma	1	1.18 (0.07, 19.7)	1	1.51 (0.17, 13.5)	1	0.92 (0.02, 46.3)	0	N/A	0	N/A	0	N/A
Calcification	730	1.39 (1.24, 1.57)	518	1.31 (1.14, 1.50)	523	1.32 (1.15, 1.51)	226	1.66 (1.33, 2.07)	138	1.30 (0.99, 1.69)	100	1.06 (0.80, 1.40) ^b
Phyllodes	7	1.52 (0.60, 3.80)	7	1.16 (0.35, 3.80)	9	3.23 (1.48, 7.06)	8	5.76 (2.37, 14.0)	2	2.22 (0.44, 11.2)	2	1.59 (0.18, 14.4)
Fibrosis	463	1.52 (1.32, 1.76)	259	1.07 (0.90, 1.27) ^b	220	1.02 (0.85, 1.22) ^b	132	1.16 (0.88, 1.54)	77	1.17 (0.84, 1.62)	34	0.72 (0.47, 1.10)
Epithelial benign	26	1.19 (0.75, 1.88)	32	1.43 (0.92, 2.21)	34	1.23 (0.82, 1.85)	6	0.94 (0.34, 2.59)	10	2.04 (0.97, 4.25)	6	0.89 (0.32, 2.43)
Sclerosing adenosis	111	1.08 (0.85, 1.38)	90	1.28 (0.97, 1.69)	59	1.24 (0.87, 1.76)	54	1.37 (0.93, 2.01)	33	1.31 (0.78, 2.19)	17	1.59 (0.81, 3.12)
Hamartoma	1	0.69 (0.04, 11.2)	1	1.58 (0.22, 11.3)	1	1.49 (0.21, 10.4)	0	N/A	1	5.23 (0.72, 37.9)	0	N/A
Cyst	242	1.18 (0.97, 1.43)	162	1.03 (0.82, 1.29)	135	1.17 (0.91, 1.51)	89	1.41 (1.02, 1.95)	43	1.07 (0.69, 1.64)	34	1.20 (0.70, 2.07)
Inflammation	149	1.10 (0.88, 1.36)	89	1.09 (0.84, 1.42)	72	0.87 (0.66, 1.16)	41	1.00 (0.66, 1.51)	28	1.00 (0.60, 1.67)	21	1.38 (0.83, 2.30)
Skin	2	1.11 (0.16, 7.90)	1	1.08 (0.07, 17.2)	0	N/A	3	9.47 (2.82, 31.8)	0	N/A	0	N/A
Apocrine Metaplasia	179	0.90 (0.73, 1.11)	136	0.99 (0.77, 1.26)	122	0.95 (0.73, 1.23)	68	0.99 (0.69, 1.42)	34	0.74 (0.46, 1.20)	27	0.66 (0.35, 1.26)
Stromal benign	10	1.09 (0.46, 2.57)	3	0.62 (0.18, 2.15)	7	0.67 (0.26, 1.72)	1	0.73 (0.10, 5.29)	1	0.98 (0.14, 7.12)	2	1.54 (0.39, 6.15)
Fibroadenomatous change/hyperplasia	14	0.64 (0.32, 1.27)	13	1.37 (0.72, 2.62)	6	0.83 (0.37, 1.83)	3	0.65 (0.19, 2.25)	4	0.71 (0.12, 4.03)	1	0.20 (0.01, 6.21)
Hemangioma	3	0.70 (0.13, 3.83)	2	0.78 (0.11, 5.57)	2	0.83 (0.16, 4.39)	0	N/A	1	3.13 (0.43, 22.6)	0	N/A
Atrophy	7	0.88 (0.34, 2.30)	3	0.39 (0.10, 1.60)	8	0.56 (0.24, 1.32)	1	0.52 (0.03, 8.43)	0	N/A	0	N/A

Abbreviations: BBD, benign breast disease; CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified

*HRs (95% CI) are adjusted for age (continuous)

^aHRs for specific diagnoses are adjusted for concurrent diagnoses seen in this list

[^]Women with negative/benign mammograms are the reference group in all models

S1.1 Most common combinations of BBD diagnoses within the same biopsy episode among women with multiple BBD diagnoses.

	% among biopsies		% among all				
	with >1 BBD	biopsies	BBD_1	BBD_2	BBD_3	BBD_4	BBD_5
COUNT	(n=45,752)	(n=131,075)					
3861	8.4	2.9	Calcification	Fibrocystic changes NOS			
3604	7.9	2.7	Calcification	Usual ductal hyperplasia			
2165	4.7	1.7	Calcification	Fibroadenoma			
2082	4.6	1.6	Calcification	Fibrosis			
1626	3.6	1.2	Fibrocystic changes NOS	Fibroadenoma			
1013	2.2	0.8	Fibroadenoma	Usual ductal hyperplasia			
958	2.1	0.7	Fibrosis	Inflammation			
784	1.7	0.6	Fibrosis	Usual ductal hyperplasia			
771	1.7	0.6	Calcification	Fibrosis	Usual ductal hyperplasia		
652	1.4	0.5	Cyst	Fibrosis			
638	1.4	0.5	Fibroadenoma	Fibrosis			
518	1.1	0.4	Calcification	Fibrocystic changes NOS	Fibroadenoma		
472	1.0	0.4	Calcification	Fibroadenoma	Usual ductal hyperplasia		
467	1.0	0.4	Solitary Papilloma	Usual ductal hyperplasia			
445	1.0	0.3	Cyst	Apocrine Metaplasia			
442	1.0	0.3	Cyst	Inflammation			
363	0.8	0.3	Apocrine Metaplasia	Usual ductal hyperplasia			
359	0.8	0.3	Fibrocystic changes NOS	Solitary Papilloma			
344	0.8	0.3	Fibrocystic changes NOS	Inflammation			
340	0.7	0.3	Calcification	Cyst	Fibrosis		
323	0.7	0.2	Calcification	Inflammation			
323	0.7	0.2	Calcification	Cyst			
315	0.7	0.2	Calcification	Fibroadenoma	Fibrosis		
310	0.7	0.2	Calcification	Apocrine Metaplasia			
287	0.6	0.2	Fibrosis	Apocrine Metaplasia			
278	0.6	0.2	Adenosis	Calcification			
267	0.6	0.2	Calcification	Solitary Papilloma	Usual ductal hyperplasia		
244	0.5	0.2	Calcification	Fibrosis	Inflammation		

242	0.5	0.2	Cyst	Fibrosis	Inflammation	
236	0.5	0.2	Adenosis	Fibrosis		
229	0.5	0.2	Cyst	Usual ductal hyperplasia		
210	0.5	0.2	Calcification	Apocrine Metaplasia	Usual ductal hyperplasia	
208	0.5	0.2	Adenosis	Usual ductal hyperplasia		
206	0.5	0.2	Sclerosing adenosis	Fibroadenoma		
199	0.4	0.2	Calcification	Sclerosing adenosis		
196	0.4	0.1	Cyst	Fibrosis	Apocrine Metaplasia	
196	0.4	0.1	Adenosis	Apocrine Metaplasia		
195	0.4	0.1	Sclerosing adenosis	Fibrosis		
193	0.4	0.1	Fibrosis	Solitary Papilloma		
191	0.4	0.1	Calcification	Columnar cell lesions		
187	0.4	0.1	Adenosis	Fibroadenoma		
185	0.4	0.1	Fibroadenoma	Apocrine Metaplasia		
175	0.4	0.1	Calcification	Sclerosing adenosis Pseudoangiomatous	Fibrosis	
172	0.4	0.1	Fibrocystic changes NOS	stromal hyperplasia		
168	0.4	0.1	Sclerosing adenosis	Usual ductal hyperplasia		
161	0.4	0.1	Calcification	Fibrosis	Apocrine Metaplasia	
159	0.3	0.1	Calcification	Cyst	Fibrosis	Usual ductal hyperplasia
150	0.3	0.1	Calcification	Cyst	Fibrosis	Apocrine Metaplasia
149	0.3	0.1	Cyst	Fibrosis	Usual ductal hyperplasia	
148	0.3	0.1	Adenosis	Sclerosing adenosis		
143	0.3	0.1	Calcification	Cyst	Usual ductal hyperplasia	
141	0.3	0.1	Adenosis	Calcification	Usual ductal hyperplasia	
135	0.3	0.1	Cyst	Apocrine Metaplasia	Usual ductal hyperplasia	
134	0.3	0.1	Calcification	Cyst	Apocrine Metaplasia	
132	0.3	0.1	Adenosis	Calcification	Fibrosis	
126	0.3	0.1	Calcification	Fibrosis	Apocrine Metaplasia	Usual ductal hyperplasia
125	0.3	0.1	Usual ductal hyperplasia	Inflammation		
121	0.3	0.1	Cyst	Fibrosis	Apocrine Metaplasia	Usual ductal hyperplasia
120	0.3	0.1	Apocrine Metaplasia	Solitary Papilloma		

120	0.3	0.1	Cyst	Fibroadenoma		
119	0.3	0.1	Fibrosis	Apocrine Metaplasia	Usual ductal hyperplasia	
116	0.3	0.1	Calcification	Solitary Papilloma		
116	0.3	0.1	Calcification	Fibrocystic changes NOS	Solitary Papilloma	
				Pseudoangiomatous		
110	0.2	0.1	Fibrosis	stromal hyperplasia		
109	0.2	0.1	Fibroadenoma	Fibrosis	Usual ductal hyperplasia	
108	0.2	0.1	Fibrosis	Solitary Papilloma	Usual ductal hyperplasia	
				Fibroadenomatous		
106	0.2	0.1	Calcification	change/hyperplasia		
106	0.2	0.1	Calcification	Fibrocystic changes NOS	Inflammation	
104	0.2	0.1	Fibrocystic changes NOS	Radial scar		
104	0.2	0.1	Calcification	Fibroadenoma	Fibrosis	Usual ductal hyperplasia
103	0.2	0.1	Sclerosing adenosis	Fibrosis	Usual ductal hyperplasia	
100	0.2	0.1	Calcification	Cyst	Apocrine Metaplasia	Usual ductal hyperplasia
			Benign breast			
99	0.2	0.1	parenchyma	Inflammation		
97	0.2	0.1	Calcification	Sclerosing adenosis	Fibrosis	Usual ductal hyperplasia
96	0.2	0.1	Columnar cell lesions	Fibrosis		
94	0.2	0.1	Adenosis	Cyst		
94	0.2	0.1	Adenosis	Calcification	Apocrine Metaplasia	Usual ductal hyperplasia
				Pseudoangiomatous		
93	0.2	0.1	Fibroadenoma	stromal hyperplasia		
90	0.2	0.1	Benign NOS	Inflammation		
88	0.2	0.1	Calcification	Sclerosing adenosis	Usual ductal hyperplasia	
88	0.2	0.1	Calcification	Columnar cell lesions	Fibrosis	
87	0.2	0.1	Calcification	Cyst	Fibrosis	Apocrine Metaplasia
						Usual ductal hyperplasia
86	0.2	0.1	Fibroadenoma	Inflammation		
86	0.2	0.1	Sclerosing adenosis	Apocrine Metaplasia		
86	0.2	0.1	Calcification	Fibrosis	Solitary Papilloma	Usual ductal hyperplasia
81	0.2	0.1	Adenosis	Apocrine Metaplasia	Usual ductal hyperplasia	
79	0.2	0.1	Calcification	Sclerosing adenosis	Fibroadenoma	
78	0.2	0.1	Columnar cell lesions	Fibrosis	Usual ductal hyperplasia	

76	0.2	0.1	Pseudoangiomatous stromal hyperplasia	Usual ductal hyperplasia		
75	0.2	0.1	Radial scar	Usual ductal hyperplasia		
75	0.2	0.1	Apocrine Metaplasia	Inflammation		
75	0.2	0.1	Calcification	Radial scar	Usual ductal hyperplasia	
75	0.2	0.1	Calcification	Columnar cell lesions	Fibrosis	Usual ductal hyperplasia
75	0.2	0.1	Adenosis	Cyst	Fibrosis	
73	0.2	0.1	Fibroadenoma	Apocrine Metaplasia	Usual ductal hyperplasia	
72	0.2	0.1	Adenosis	Calcification	Fibroadenoma	
71	0.2	0.1	Fibroadenoma	Fibroadenomatous change/hyperplasia		
71	0.2	0.1	Adenosis	Calcification	Sclerosing adenosis	
69	0.2	0.1	Calcification	Fibrosis	Solitary Papilloma	
68	0.1	0.1	Fibrocystic changes NOS	Epithelial benign		

Percentages are presented in two ways:

1. Relative frequency among biopsies with >1 BBD diagnosis (i.e., how common the combination is within multi-diagnosis biopsies).
2. Proportion of all biopsies in the study (i.e., how common the combination is overall).

Only the top 100 combinations are shown.

S1.2. Most common combinations of BBD diagnoses including columnar cell lesions within the same biopsy episode

COUNT	% among biopsies with columnar cell lesions (n=2,584)	% among all biopsies (n=131,075)	BBD_1	BBD_2	BBD_3	BBD_4
191	7.4	0.1	Calcification			
96	3.7	0.1	Fibrosis			
88	3.4	0.1	Calcification	Fibrosis		
78	3.0	0.1	Fibrosis	Usual ductal hyperplasia		
75	2.9	0.1	Calcification	Fibrosis	Usual ductal hyperplasia	
66	2.6	0.1	Calcification	Usual ductal hyperplasia		
54	2.1	0.0	Usual ductal hyperplasia			
41	1.6	0.0	Cyst			
40	1.5	0.0	Calcification	Sclerosing adenosis	Fibrosis	
38	1.5	0.0	Calcification	Sclerosing adenosis	Fibrosis	Usual ductal hyperplasia
34	1.3	0.0	Calcification	Cyst	Fibrosis	
30	1.2	0.0	Calcification	Cyst	Fibrosis	Usual ductal hyperplasia
29	1.1	0.0	Apocrine Metaplasia Pseudoangiomatous stromal hyperplasia			
25	1.0	0.0	Sclerosing adenosis			
24	0.9	0.0	Calcification	Cyst		
23	0.9	0.0	Cyst	Fibrosis		
22	0.9	0.0	Cyst	Fibrosis	Usual ductal hyperplasia	
22	0.9	0.0	Calcification	Apocrine Metaplasia		
21	0.8	0.0	Cyst	Usual ductal hyperplasia		
21	0.8	0.0	Cyst	Fibrosis	Apocrine Metaplasia	
21	0.8	0.0	Calcification	Apocrine Metaplasia	Usual ductal hyperplasia	
21	0.8	0.0	Calcification	Cyst	Fibrosis	Apocrine Metaplasia
20	0.8	0.0	Apocrine Metaplasia	Usual ductal hyperplasia		
20	0.8	0.0	Calcification	Sclerosing adenosis	Usual ductal hyperplasia	
19	0.7	0.0	Sclerosing adenosis	Fibrosis		
19	0.7	0.0	Cyst	Fibrosis	Apocrine Metaplasia	Usual ductal hyperplasia
19	0.7	0.0	Adenosis	Calcification		

18	0.7	0.0	Fibrosis	Apocrine Metaplasia
18	0.7	0.0	Fibroadenoma	

Percentages are presented in two ways:

1. Relative frequency among biopsies with >1 BBD diagnosis (i.e., how common the combination is within multi-diagnosis biopsies).
2. Proportion of all biopsies in the study (i.e., how common the combination is overall).

Only the top 30 combinations are shown.

S1.3. Most common combinations of BBD diagnoses including papillomatosis within the same biopsy episode

COUNT	% among biopsies with papillomatosis (n=601)	% among all biopsies (n=131,075)	BBD_1	BBD_2	BBD_3	BBD_4	BBD_5
28	4.7	0.0	Apocrine Metaplasia				
24	4.0	0.0	Calcification	Apocrine Metaplasia	Usual ductal hyperplasia		
23	3.8	0.0	Solitary Papilloma				
20	3.3	0.0	Calcification	Cyst	Apocrine Metaplasia		
			Fibrocystic changes				
19	3.2	0.0	NOS				
				Usual ductal			
19	3.2	0.0	Calcification	hyperplasia			
			Usual ductal				
15	2.5	0.0	hyperplasia				
15	2.5	0.0	Calcification	Cyst	Apocrine Metaplasia	Usual ductal hyperplasia	
				Usual ductal			
14	2.3	0.0	Apocrine Metaplasia	hyperplasia			
12	2.0	0.0	Cyst	Apocrine Metaplasia			
11	1.8	0.0	Calcification	Apocrine Metaplasia			
10	1.7	0.0	Cyst	Apocrine Metaplasia	Usual ductal hyperplasia		
9	1.5	0.0	Adenosis	Calcification	Usual ductal hyperplasia		
7	1.2	0.0	Fibrosis				
7	1.2	0.0	Fibrosis	Apocrine Metaplasia	Usual ductal hyperplasia		
7	1.2	0.0	Cyst				
7	1.2	0.0	Adenosis	Calcification	Apocrine Metaplasia	Usual ductal hyperplasia	
6	1.0	0.0	Sclerosing adenosis				
				Usual ductal			
5	0.8	0.0	Fibroadenoma	hyperplasia			
5	0.8	0.0	Cyst	Apocrine Metaplasia	Solitary Papilloma	Usual ductal hyperplasia	
5	0.8	0.0	Cyst	Fibrosis	Apocrine Metaplasia		
5	0.8	0.0	Calcification	Fibrosis	Usual ductal hyperplasia		
				Fibrocystic changes			
5	0.8	0.0	Calcification	NOS			
5	0.8	0.0	Adenosis				

5	0.8	0.0	Adenosis	Calcification	Sclerosing adenosis	Apocrine Metaplasia	
5	0.8	0.0	Adenosis	Calcification	Cyst	Sclerosing adenosis	Apocrine Metaplasia
4	0.7	0.0	Inflammation				
4	0.7	0.0	Apocrine Metaplasia	Solitary Papilloma			
4	0.7	0.0	Apocrine Metaplasia	Solitary Papilloma	Usual ductal hyperplasia		
4	0.7	0.0	Fibrosis	Usual ductal hyperplasia			

Percentages are presented in two ways:

1. Relative frequency among biopsies with >1 BBD diagnosis (i.e., how common the combination is within multi-diagnosis biopsies).
2. Proportion of all biopsies in the study (i.e., how common the combination is overall).

Only the top 30 combinations are shown.

S1.4. Most common combinations of BBD diagnoses including atrophy within the same biopsy episode

COUNT	% among biopsies with atrophy (n=281)	% among all biopsies (n=131,075)	BBD_1	BBD_2	BBD_3
55	19.6	0.0	Calcification	Fibrosis	
41	14.6	0.0	Calcification		
30	10.7	0.0	Fibrosis		
29	10.3	0.0	Calcification	Fibroadenoma	
9	3.2	0.0	Calcification	Inflammation	
8	2.8	0.0	Inflammation		
8	2.8	0.0	Calcification	Fibroadenoma	Fibrosis
7	2.5	0.0	Calcification	Fibroadenoma	Fibroadenomatous change/hyperplasia
6	2.1	0.0	Fibrosis	Inflammation	
6	2.1	0.0	Calcification	Apocrine Metaplasia	
6	2.1	0.0	Calcification	Fibrosis	Inflammation
5	1.8	0.0	Calcification	Cyst	
4	1.4	0.0	Fibroadenoma		
4	1.4	0.0	Calcification	Cyst	Inflammation
3	1.1	0.0	Calcification	Fibroadenoma	Inflammation
3	1.1	0.0	Calcification	Fibrocystic changes NOS	
2	0.7	0.0	Apocrine Metaplasia		
2	0.7	0.0	Fibrosis	Usual ductal hyperplasia	
2	0.7	0.0	Fibroadenoma	Fibrosis	
2	0.7	0.0	Cyst	Fibrosis	Apocrine Metaplasia
2	0.7	0.0	Calcification	Usual ductal hyperplasia	
2	0.7	0.0	Calcification	Stromal benign	
2	0.7	0.0	Calcification	Fibrosis	Stromal benign
2	0.7	0.0	Calcification	Fibroadenoma	Usual ductal hyperplasia
2	0.7	0.0	Calcification	Cyst	Fibrosis
1	0.4	0.0	Usual ductal hyperplasia		
1	0.4	0.0	Solitary Papilloma		
1	0.4	0.0	Apocrine Metaplasia	Papillomatosis	

1	0.4	0.0	Apocrine Metaplasia	Usual ductal hyperplasia
1	0.4	0.0	Fibroadenoma	Inflammation

Percentages are presented in two ways:

1. Relative frequency among biopsies with >1 BBD diagnosis (i.e., how common the combination is within multi-diagnosis biopsies).
2. Proportion of all biopsies in the study (i.e., how common the combination is overall).

Only the top 30 combinations are shown.

S1.5. Most common combinations of BBD diagnoses including calcifications within the same biopsy episode

COUNT	% among biopsies with calcifications (n=24,621)	% among all biopsies (n=131,075)	BBD_1	BBD_2	BBD_3
3861	15.7	2.9	Fibrocystic changes NOS		
3604	14.6	2.7	Usual ductal hyperplasia		
2165	8.8	1.7	Fibroadenoma		
2082	8.5	1.6	Fibrosis		
771	3.1	0.6	Fibrosis	Usual ductal hyperplasia	
518	2.1	0.4	Fibrocystic changes NOS	Fibroadenoma	
472	1.9	0.4	Fibroadenoma	Usual ductal hyperplasia	
340	1.4	0.3	Cyst	Fibrosis	
323	1.3	0.2	Inflammation		
323	1.3	0.2	Cyst		
315	1.3	0.2	Fibroadenoma	Fibrosis	
310	1.3	0.2	Apocrine Metaplasia		
278	1.1	0.2	Adenosis		
267	1.1	0.2	Solitary Papilloma	Usual ductal hyperplasia	
244	1.0	0.2	Fibrosis	Inflammation	
210	0.9	0.2	Apocrine Metaplasia	Usual ductal hyperplasia	
199	0.8	0.2	Sclerosing adenosis		
191	0.8	0.1	Columnar cell lesions		
175	0.7	0.1	Sclerosing adenosis	Fibrosis	
161	0.7	0.1	Fibrosis	Apocrine Metaplasia	
159	0.6	0.1	Cyst	Fibrosis	Usual ductal hyperplasia
150	0.6	0.1	Cyst	Fibrosis	Apocrine Metaplasia
143	0.6	0.1	Cyst	Usual ductal hyperplasia	
141	0.6	0.1	Adenosis	Usual ductal hyperplasia	
134	0.5	0.1	Cyst	Apocrine Metaplasia	
132	0.5	0.1	Adenosis	Fibrosis	
126	0.5	0.1	Fibrosis	Apocrine Metaplasia	Usual ductal hyperplasia
116	0.5	0.1	Solitary Papilloma		

116	0.5	0.1	Fibrocystic changes NOS	Solitary Papilloma
106	0.4	0.1	Fibroadenomatous change/hyperplasia	

Percentages are presented in two ways:

1. Relative frequency among biopsies with >1 BBD diagnosis (i.e., how common the combination is within multi-diagnosis biopsies).
2. Proportion of all biopsies in the study (i.e., how common the combination is overall).

Only the top 30 combinations are shown.

S1.6. Most common combinations of BBD diagnoses including sclerosing adenosis within the same biopsy episode

COUNT	% among biopsies with sclerosing adenosis (n=4,708)	% among all biopsies (n=131,075)	BBD_1	BBD_2	BBD_3	BBD_4
206	4.4	0.2	Fibroadenoma			
199	4.2	0.2	Calcification			
195	4.1	0.1	Fibrosis			
175	3.7	0.1	Calcification	Fibrosis		
168	3.6	0.1	Usual ductal hyperplasia			
148	3.1	0.1	Adenosis			
103	2.2	0.1	Fibrosis	Usual ductal hyperplasia		
97	2.1	0.1	Calcification	Fibrosis	Usual ductal hyperplasia	
88	1.9	0.1	Calcification	Usual ductal hyperplasia		
86	1.8	0.1	Apocrine Metaplasia			
79	1.7	0.1	Calcification	Fibroadenoma		
71	1.5	0.1	Adenosis	Calcification		
61	1.3	0.0	Cyst			
58	1.2	0.0	Calcification	Cyst	Fibrosis	
58	1.2	0.0	Calcification	Cyst	Fibrosis	Usual ductal hyperplasia
54	1.1	0.0	Apocrine Metaplasia	Usual ductal hyperplasia		
46	1.0	0.0	Calcification	Apocrine Metaplasia		
46	1.0	0.0	Adenosis	Calcification	Usual ductal hyperplasia	
45	1.0	0.0	Solitary Papilloma			
43	0.9	0.0	Fibroadenoma	Usual ductal hyperplasia		
42	0.9	0.0	Cyst	Fibrosis		
42	0.9	0.0	Calcification	Fibroadenoma	Fibrosis	
42	0.9	0.0	Calcification	Cyst		
40	0.8	0.0	Calcification	Columnar cell lesions	Fibrosis	
38	0.8	0.0	Calcification	Fibrosis	Apocrine Metaplasia	Usual ductal hyperplasia
38	0.8	0.0	Calcification	Cyst	Usual ductal hyperplasia	
38	0.8	0.0	Calcification	Columnar cell lesions	Fibrosis	Usual ductal hyperplasia
37	0.8	0.0	Fibroadenoma	Fibrosis		

37	0.8	0.0	Cyst	Usual ductal hyperplasia		
35	0.7	0.0	Adenosis	Calcification	Apocrine Metaplasia	Usual ductal hyperplasia

Percentages are presented in two ways:

1. Relative frequency among biopsies with >1 BBD diagnosis (i.e., how common the combination is within multi-diagnosis biopsies).
2. Proportion of all biopsies in the study (i.e., how common the combination is overall).

Only the top 30 combinations are shown.

S1.7. Most common combinations of BBD diagnoses including apocrine metaplasia within the same biopsy episode

COUNT	% among biopsies with apocrine metaplasia (n=8,215)	% among all biopsies (n=131,075)	BBD_1	BBD_2	BBD_3	BBD_4
445	5.4	0.3	Cyst			
363	4.4	0.3	Usual ductal hyperplasia			
310	3.8	0.2	Calcification			
287	3.5	0.2	Fibrosis			
210	2.6	0.2	Calcification	Usual ductal hyperplasia		
196	2.4	0.1	Cyst	Fibrosis		
196	2.4	0.1	Adenosis			
185	2.3	0.1	Fibroadenoma			
161	2.0	0.1	Calcification	Fibrosis		
150	1.8	0.1	Calcification	Cyst	Fibrosis	
135	1.6	0.1	Cyst	Usual ductal hyperplasia		
134	1.6	0.1	Calcification	Cyst		
126	1.5	0.1	Calcification	Fibrosis	Usual ductal hyperplasia	
121	1.5	0.1	Cyst	Fibrosis	Usual ductal hyperplasia	
120	1.5	0.1	Solitary Papilloma			
119	1.4	0.1	Fibrosis	Usual ductal hyperplasia		
100	1.2	0.1	Calcification	Cyst	Usual ductal hyperplasia	
94	1.1	0.1	Adenosis	Calcification	Usual ductal hyperplasia	
87	1.1	0.1	Calcification	Cyst	Fibrosis	Usual ductal hyperplasia
86	1.0	0.1	Sclerosing adenosis			
81	1.0	0.1	Adenosis	Usual ductal hyperplasia		
75	0.9	0.1	Inflammation			
73	0.9	0.1	Fibroadenoma	Usual ductal hyperplasia		
64	0.8	0.0	Adenosis	Calcification		
61	0.7	0.0	Solitary Papilloma	Usual ductal hyperplasia		
58	0.7	0.0	Calcification	Fibroadenoma		
58	0.7	0.0	Adenosis	Cyst		
54	0.7	0.0	Sclerosing adenosis	Usual ductal hyperplasia		

52	0.6	0.0	Pseudoangiomatous stromal hyperplasia		
48	0.6	0.0	Cyst	Fibrosis	Inflammation

Percentages are presented in two ways:

1. Relative frequency among biopsies with >1 BBD diagnosis (i.e., how common the combination is within multi-diagnosis biopsies).
2. Proportion of all biopsies in the study (i.e., how common the combination is overall).

Only the top 30 combinations are shown.

S1.8. Most common combinations of BBD diagnoses including adenosis within the same biopsy episode

COUNT	% among biopsies with adenosis (n=5,268)	% among all biopsies (n=131,724)	BBD_1	BBD_2	BBD_3	BBD_4
278	5.3	0.2	Calcification			
236	4.5	0.2	Fibrosis			
208	3.9	0.2	Usual ductal hyperplasia			
196	3.7	0.1	Apocrine Metaplasia			
187	3.5	0.1	Fibroadenoma			
148	2.8	0.1	Sclerosing adenosis			
141	2.7	0.1	Calcification	Usual ductal hyperplasia		
132	2.5	0.1	Calcification	Fibrosis		
94	1.8	0.1	Cyst			
94	1.8	0.1	Calcification	Apocrine Metaplasia	Usual ductal hyperplasia	
81	1.5	0.1	Apocrine Metaplasia	Usual ductal hyperplasia		
75	1.4	0.1	Cyst	Fibrosis		
72	1.4	0.1	Calcification	Fibroadenoma		
71	1.3	0.1	Calcification	Sclerosing adenosis		
64	1.2	0.0	Calcification	Apocrine Metaplasia		
62	1.2	0.0	Calcification	Cyst	Fibrosis	
59	1.1	0.0	Pseudoangiomatous stromal hyperplasia			
59	1.1	0.0	Calcification	Cyst		
58	1.1	0.0	Cyst	Apocrine Metaplasia		
51	1.0	0.0	Calcification	Cyst	Usual ductal hyperplasia	
50	0.9	0.0	Calcification	Fibrosis	Usual ductal hyperplasia	
48	0.9	0.0	Calcification	Cyst	Fibrosis	Usual ductal hyperplasia
47	0.9	0.0	Fibrosis	Apocrine Metaplasia		
46	0.9	0.0	Calcification	Sclerosing adenosis	Usual ductal hyperplasia	
43	0.8	0.0	Cyst	Fibrosis	Usual ductal hyperplasia	
43	0.8	0.0	Cyst	Fibrosis	Apocrine Metaplasia	
42	0.8	0.0	Fibroadenoma	Usual ductal hyperplasia		

41	0.8	0.0	Fibrosis	Usual ductal hyperplasia	
40	0.8	0.0	Cyst	Usual ductal hyperplasia	
40	0.8	0.0	Calcification	Fibrosis	Apocrine Metaplasia

Percentages are presented in two ways:

1. Relative frequency among biopsies with >1 BBD diagnosis (i.e., how common the combination is within multi-diagnosis biopsies).
2. Proportion of all biopsies in the study (i.e., how common the combination is overall).

Only the top 30 combinations are shown.

S1.9. Hazards ratios (HR) and 95% confidence intervals for the association between benign breast disease diagnoses and subsequent invasive carcinoma.

	Invasive breast cancer					
	Case No.	HR (95% CI) ^{*,a}	Case No.	HR (95% CI) ^{*,a,b}	Case No.	HR(95% CI) ^{*,a,b,c}
Negative mammogram	30,185	Referent [^]	20,489	Referent [^]	12,570	Referent [^]
Lobular Carcinoma <i>in situ</i>	77	5.61 (4.10, 7.68)	66	4.84 (3.40, 6.89)	51	4.85 (3.24, 7.25)
Proliferative changes with Atypia	544	4.10 (3.66, 4.59)	424	3.43 (3.00, 3.91)	265	3.50 (2.97, 4.12)
Atypical lobular hyperplasia	139	4.85 (3.92, 6.02)	104	3.61 (2.79, 4.67)	73	3.94 (2.89, 5.37)
Atypical ductal hyperplasia	288	3.91 (3.33, 4.58)	231	3.55 (2.97, 4.24)	151	3.42 (2.75, 4.26)
Atypical hyperplasia mixed	17	3.79 (1.97, 7.30)	14	3.06 (1.50, 6.25)	10	3.50 (1.49, 8.24)
Atypical hyperplasia NOS	71	3.74 (2.74, 5.11)	50	2.89 (1.96, 4.27)	16	3.10 (1.68, 5.72)
Atypia NOS	25	3.17 (1.91, 5.27)	21	2.46 (1.39, 4.35)	14	2.66 (1.33, 5.32)
Papillary with atypia	9	2.76 (0.92, 8.29)	9	2.85 (0.91, 8.89)	3	1.57 (0.24, 10.22)
Proliferative changes without Atypia	1176	1.51 (1.39, 1.64)	939	1.46 (1.33, 1.60)	607	1.43 (1.27, 1.61)
Multiple papillomas	18	2.84 (1.60, 5.05)	14	2.34 (1.20, 4.56)	7	2.02 (0.84, 4.86)
Solitary Papilloma	298	1.68 (1.44, 1.95)	229	1.60 (1.34, 1.92)	121	1.45 (1.13, 1.85)
Flat Epithelial Atypia	10	1.63 (0.69, 3.87)	10	1.60 (0.67, 3.81)	4	1.08 (0.28, 4.13)
Usual ductal hyperplasia	890	1.55 (1.39, 1.72)	722	1.50 (1.34, 1.69)	489	1.47 (1.28, 1.70)
Radial scar	51	1.24 (0.85, 1.81)	39	1.12 (0.73, 1.71)	30	1.44 (0.89, 2.31)
Columnar cell lesions	67	1.22 (0.87, 1.70)	64	1.27 (0.90, 1.79)	58	1.43 (0.99, 2.08)
Papillomatosis	27	1.06 (0.66, 1.70)	22	1.13 (0.66, 1.94)	6	1.14 (0.38, 3.40)
Nonproliferative Lesions	4089	1.90 (1.82, 1.99)	3171	1.74 (1.65, 1.83)	1904	1.64 (1.53, 1.75)
Benign breast parenchyma	119	2.16 (1.74, 2.68)	87	2.03 (1.57, 2.62)	37	1.79 (1.21, 2.65)
Fibrocystic changes NOS	1038	1.94 (1.79, 2.10)	724	1.72 (1.56, 1.90)	403	1.54 (1.35, 1.76)
Benign NOS	233	1.89 (1.62, 2.21)	205	1.66 (1.40, 1.97)	169	1.74 (1.44, 2.10)
Adenoma	8	1.87 (0.86, 4.07)	6	1.56 (0.61, 4.02)	3	2.12 (0.61, 7.37)
Adenosis	306	1.64 (1.41, 1.91)	212	1.45 (1.21, 1.73)	94	1.37 (1.04, 1.79)
Benign stromal neoplasm	28	1.62 (1.03, 2.55)	20	1.55 (0.88, 2.73)	8	1.20 (0.44, 3.26)
Pseudoangiomatous stromal hyperplasia	51	1.42 (1.00, 2.02)	45	1.34 (0.92, 1.95)	33	1.83 (1.19, 2.81)
Squamous Metaplasia	1	1.39 (0.19, 10.48)	0	0.00 (0.00, 0.00)	0	0.00 (0.00, 0.00)

Fibroadenoma	903	1.39 (1.28, 1.51)	716	1.35 (1.23, 1.48)	425	1.29 (1.14, 1.46)
Adenomyoepithelioma	2	1.38 (0.22, 8.82)	2	1.59 (0.24, 10.78)	1	1.37 (0.08, 24.58)
Calcification	1248	1.35 (1.23, 1.48)	1018	1.28 (1.16, 1.42)	646	1.23 (1.08, 1.40)
Phyllodes	14	1.34 (0.64, 2.79)	14	1.54 (0.74, 3.21)	10	1.31 (0.51, 3.39)
Fibrosis	722	1.31 (1.17, 1.46)	610	1.32 (1.17, 1.49)	381	1.35 (1.15, 1.58)
Epithelial benign	58	1.30 (0.94, 1.78)	37	1.43 (0.95, 2.14)	6	0.79 (0.29, 2.14)
Sclerosing adenosis	201	1.15 (0.96, 1.39)	163	1.02 (0.83, 1.25)	96	1.17 (0.89, 1.55)
Hamartoma	2	1.13 (0.23, 5.58)	2	1.45 (0.29, 7.17)	1	1.00 (0.06, 16.61)
Cyst	404	1.12 (0.97, 1.30)	330	1.10 (0.94, 1.30)	172	0.99 (0.78, 1.26)
Inflammation	238	1.09 (0.92, 1.29)	180	1.02 (0.84, 1.25)	105	0.97 (0.74, 1.26)
Skin	3	1.07 (0.21, 5.31)	2	0.79 (0.11, 5.72)	1	0.62 (0.04, 10.18)
Apocrine Metaplasia	315	0.94 (0.80, 1.10)	250	0.92 (0.77, 1.10)	127	0.90 (0.69, 1.18)
Stromal benign	13	0.89 (0.44, 1.80)	10	1.00 (0.44, 2.25)	10	1.09 (0.48, 2.45)
Fibroadenomatous						
change/hyperplasia	27	0.88 (0.54, 1.41)	24	0.87 (0.52, 1.45)	13	0.92 (0.47, 1.83)
Hemangioma	5	0.74 (0.20, 2.68)	4	0.85 (0.20, 3.63)	4	1.64 (0.39, 6.95)
Atrophy	10	0.63 (0.28, 1.40)	9	0.75 (0.32, 1.73)	1	1.25 (0.17, 9.12)

Abbreviations: BBD, benign breast disease; CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified

*HRs (95% CI) are adjusted for age (continuous)

^aHRs for specific diagnoses are adjusted for concurrent diagnoses seen in this list

[^]Women with negative/benign mammograms are the reference group in all models

^bHRs adjusted for breast density, ethnicity, and family history of breast cancer are calculated from a subset of women with available data for all of these variables

^cHRs additionally adjusted for body mass index, as well as variables mentioned above

S1.10. Hazards ratios (HR) and 95% confidence intervals for the association between benign breast disease diagnoses and subsequent DCIS.

	DCIS					
	Case No.	HR (95% CI) ^{*,a}	Case No.	HR ^{*,a,b}	Case No.	HR ^{*,a,b,c}
Negative mammogram	8,069	Referent [^]	5,488	Referent [^]	3,368	Referent [^]
Lobular Carcinoma <i>in situ</i>	29	8.82 (5.39, 14.41)	26	8.86 (5.25, 14.94)	22	9.26 (5.08, 16.88)
Proliferative changes with Atypia	231	6.18 (5.16, 7.39)	185	5.63 (4.60, 6.89)	114	5.41 (4.16, 7.03)
Atypical lobular hyperplasia	41	5.07 (3.40, 7.55)	33	4.10 (2.58, 6.53)	18	3.46 (1.83, 6.57)
Atypical ductal hyperplasia	136	6.41 (5.04, 8.16)	102	5.84 (4.44, 7.67)	69	5.29 (3.72, 7.51)
Atypical hyperplasia mixed	12	8.51 (3.60, 20.09)	12	8.49 (3.56, 20.23)	9	11.46 (4.34, 30.3)
Atypical hyperplasia NOS	25	6.20 (3.72, 10.33)	21	6.18 (3.48, 10.97)	5	5.54 (1.95, 15.76)
Atypia NOS	14	5.14 (2.55, 10.37)	14	5.04 (2.51, 10.13)	11	6.60 (3.10, 14.05)
Papillary with atypia	4	5.53 (1.21, 25.23)	4	5.44 (1.19, 24.81)	3	7.31 (1.37, 39.06)
Proliferative changes without Atypia	474	2.40 (2.08, 2.76)	358	2.11 (1.79, 2.48)	246	2.16 (1.76, 2.66)
Multiple papillomas	12	5.04 (2.31, 11.00)	11	5.20 (2.30, 11.72)	7	4.89 (1.71, 13.93)
Solitary Papilloma	168	3.29 (2.61, 4.16)	114	2.72 (2.05, 3.60)	69	2.70 (1.86, 3.92)
Flat Epithelial Atypia	6	3.06 (1.00, 9.41)	4	1.96 (0.49, 7.90)	4	2.88 (0.67, 12.33)
Usual ductal hyperplasia	293	1.73 (1.42, 2.12)	230	1.60 (1.27, 2.01)	162	1.54 (1.15, 2.04)
Radial scar	30	1.54 (0.87, 2.72)	23	1.36 (0.69, 2.66)	18	1.51 (0.70, 3.26)
Columnar cell lesions	29	1.51 (0.88, 2.59)	27	1.59 (0.91, 2.79)	26	1.84 (1.01, 3.34)
Papillomatosis	9	1.37 (0.64, 2.93)	7	1.31 (0.53, 3.24)	1	0.47 (0.03, 7.52)
Nonproliferative Lesions	1242	1.86 (1.70, 2.02)	956	1.76 (1.59, 1.94)	604	1.76 (1.55, 2.00)
Benign breast parenchyma	30	1.84 (1.17, 2.89)	24	1.94 (1.16, 3.26)	10	1.60 (0.70, 3.66)
Fibrocystic changes NOS	287	1.79 (1.54, 2.09)	191	1.60 (1.32, 1.93)	126	1.65 (1.29, 2.09)
Benign NOS	88	2.66 (2.06, 3.45)	75	2.30 (1.73, 3.06)	53	2.10 (1.49, 2.97)
Adenoma	1	0.42 (0.03, 6.77)	1	0.55 (0.03, 9.14)	1	1.36 (0.08, 22.22)
Adenosis	86	1.30 (0.97, 1.75)	62	1.15 (0.81, 1.64)	32	1.34 (0.82, 2.17)
Benign stromal neoplasm	8	1.75 (0.78, 3.92)	5	1.85 (0.70, 4.85)	2	1.76 (0.35, 8.78)
Pseudoangiomatous stromal hyperplasia	13	1.18 (0.60, 2.34)	12	1.13 (0.54, 2.33)	7	1.03 (0.39, 2.69)
Squamous Metaplasia	1	2.65 (0.16, 44.96)	1	4.79 (0.26, 88.18)	0	N/A
Fibroadenoma	269	1.39 (1.19, 1.61)	211	1.35 (1.14, 1.61)	125	1.27 (1.01, 1.59)

Adenomyoepithelioma	0	N/A	0	N/A	0	N/A
Calcification	364	1.48 (1.25, 1.76)	293	1.46 (1.20, 1.77)	207	1.53 (1.20, 1.96)
Phyllodes	10	4.29 (1.96, 9.39)	8	3.43 (1.34, 8.80)	5	2.73 (0.77, 9.66)
Fibrosis	209	1.17 (0.94, 1.45)	173	1.15 (0.91, 1.46)	117	1.27 (0.94, 1.73)
Epithelial benign	16	1.46 (0.80, 2.65)	8	1.21 (0.52, 2.85)	2	1.00 (0.20, 5.14)
Sclerosing adenosis	87	1.34 (0.98, 1.83)	74	1.37 (0.97, 1.92)	50	1.84 (1.20, 2.81)
Hamartoma	1	2.57 (0.36, 18.29)	0	N/A	0	N/A
Cyst	132	1.28 (0.99, 1.66)	110	1.32 (0.99, 1.75)	56	0.93 (0.60, 1.46)
Inflammation	69	0.99 (0.72, 1.38)	55	1.08 (0.75, 1.55)	33	1.00 (0.61, 1.65)
Skin	3	6.37 (1.86, 21.83)	3	7.75 (2.28, 26.34)	3	13.22 (3.93, 44.5)
Apocrine Metaplasia	102	0.89 (0.67, 1.19)	79	0.82 (0.59, 1.15)	48	0.88 (0.54, 1.43)
Stromal benign	2	0.86 (0.21, 3.51)	1	0.64 (0.09, 4.68)	1	0.71 (0.10, 5.17)
Fibroadenomatous change/hyperplasia	7	0.66 (0.23, 1.84)	7	0.75 (0.27, 2.13)	2	0.45 (0.08, 2.57)
Hemangioma	1	1.20 (0.17, 8.56)	0	N/A	0	N/A
Atrophy	1	0.24 (0.01, 3.87)	1	0.30 (0.02, 4.93)	0	N/A

Abbreviations: BBD, benign breast disease; CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified

*HRs (95% CI) are adjusted for age (continuous)

^aHRs for specific diagnoses are adjusted for concurrent diagnoses seen in this list

[^]Women with negative/benign mammograms are the reference group in all models

^bHRs adjusted for breast density, ethnicity, and family history of breast cancer are calculated from a subset of women with available data for all of these variables

^cHRs additionally adjusted for body mass index, as well as variables mentioned above

Chapter 2: Development of a Harmonized Classification Schema for Benign Breast Disease: A Multi-Registry Approach to Standardizing Diagnostic Terminology

Olivia Sattayapiwat, Alexander D. Borowsky, Donald L. Weaver, Matt Ponzini, Theresa H.M. Keegan, Karla Kerlikowske, Diana L. Miglioretti

Abstract

Objectives: Variation in benign breast disease (BBD) terminology across clinical pathology reports complicates and the standardization and integration of pathology data for epidemiologic research. We developed a harmonized framework for BBD classification across multiple Breast Cancer Surveillance Consortium (BCSC) registries and a companion web-based application supporting research and clinical translation.

Methods: Clinical pathology records from eight BCSC registries were harmonized through an iterative, consensus-driven process. Diagnostic groupings were developed using data from a subset of registries and refined through quality control checks, additional pathology data records, and expert pathologist review. The harmonization framework incorporated structured diagnostic categories for nonspecific diagnoses, distinguished diagnostic entities from histologic descriptors, and accommodated diagnoses with multiple co-existing histologic features. Expert breast pathologists reviewed all mappings to ensure diagnostic validity, comparability, and clinical relevance.

Results: The finalized classification schema comprised 36 BBD diagnoses organized within four conventional broad classes (non-proliferative, proliferative without atypia, proliferative with atypia, and lobular carcinoma *in situ*), with four additional descriptors to capture co-occurring histologic features. The harmonization process standardized 624 unique pathology terms while preserving diagnostic detail. A web-based application was created to enable users to search individual diagnoses, identify corresponding standardized risk categories, and view related pathology terms and descriptors.

Conclusion: This harmonized BBD framework provides a standardized approach for reconciling diagnostic terminology across BCSC registries. The resulting classification schema supports integration of pathology data in consortium-based research and risk modeling, while the companion web application improves access to pathology information facilitating consistent interpretation of BBD diagnoses for use in breast cancer risk assessment.

Introduction

Over 1.6 million breast biopsies of either a palpable mass or suspicious finding on breast imaging are performed every year among U.S. women (1). Benign breast disease (BBD) is diagnosed in 75% of biopsies (2) and encompasses a diverse spectrum of diagnoses ranging from normal variations in breast tissue to proliferative changes with or without atypical features. Women with certain BBD diagnoses are at increased risk for subsequent breast cancer development, with risk varying by degree of proliferation and architectural atypia (3, 4). Accurate quantification of the level of risk associated with specific BBD diagnoses is central to the assessment and management of future breast cancer risk. However, the terminology used to describe BBD in pathology reports varies substantially across pathologists, institutions, and electronic health systems. This heterogeneity poses significant challenges for epidemiologic research, clinical decision-making, and patient understanding of their diagnosis.

Prior studies of cancer risk following BBD have generally relied on broad histologic groups defined by expert assessment of future breast cancer risk, from non-proliferative lesions (lowest risk) to proliferative changes without atypia, proliferative changes with atypia, and lobular carcinoma *in situ* (LCIS) (highest risk) (5-7, 27). While useful, these categories can obscure clinically relevant differences in risk associated with more specific pathological findings. In recent work using data from the Breast Cancer Surveillance Consortium (BCSC), we developed a harmonized set of 36 BBD diagnostic categories derived from mapping thousands of pathology terms across registries. In that work, selected pathology features were evaluated alongside diagnostic categories to further

characterize heterogeneity in breast cancer risk. We demonstrated that breast cancer risk varies substantially between specific BBD diagnosis, even within the same broad histologic category (Chapter 1), reinforcing the need for consistent diagnostic terminology and criteria that capture clinically meaningful distinctions.

This paper presents our systematic mapping of diverse pathology terms into a unified BBD classification schema comprising 36 BBD diagnoses used in our risk analysis presented in Chapter 1. We describe the development of the breast pathology data vocabulary harmonization framework and the web-based application built on this framework. The goal of this effort was to provide analytically useful and clinically relevant BBD diagnostic categories, and to create a public resource that can be used by pathologists, other clinicians, researchers, and patients. The harmonized framework can generate discussion among pathologists around the standardization of BBD terminology and inform future diagnostic guidelines. The application also can help clarify the meaning of biopsy diagnoses and provide context for associated breast cancer risk.

Development

Data sources

We used data from eight BCSC registries: Carolina Mammography Registry, Kaiser Permanente Washington Registry, Metro Chicago Breast Cancer Registry, New Hampshire Mammography Network, Northwest Screening and Cancer Outcomes Research Enterprise, Sacramento Area Breast Imaging Registry, San Francisco Mammography Registry, and Vermont Breast Cancer Surveillance System. Each registry and the statistical coordinating

center received institutional review board approval for active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analyses.

Pathology data collected on breast biopsies and breast surgeries include procedure date, procedure type, laterality, and pathology results. Diagnoses were either manually abstracted from pathology reports by trained registry staff or entered into radiology management systems by breast imaging technologists. We compiled a comprehensive list of 754 unique pathology terms from breast biopsy reports across all participating registries. After initial cleaning to resolve typographical variation and duplicate terminology, 624 unique terms were retained, capturing the wide spectrum of BBD.

Approach

Development of Diagnostic Groupings

The approach was guided by both data-driven and pathologic considerations (**Figure 1**). Initial BBD diagnostic categories were developed using data from a subset of eight BCSC registries included in the initial submission. Closely related pathologic entities were collapsed into one BBD diagnostic group (e.g., “columnar cell changes” and “columnar cell hyperplasia” into columnar cell lesions), whereas entities with sufficient sample size were considered as separate BBD diagnosis groups (e.g. “papilloma” diagnoses were respectively classified into single papilloma, multiple papillomas, and papillomatosis). Diagnostic entities (e.g., atypical ductal hyperplasia, LCIS, papilloma) were distinguished from descriptors, which included calcification, inflammation, sclerosis,

and granuloma. Descriptors were used to capture co-occurring histologic features and were not treated as independent diagnostic categories. The finalized harmonized classification schema comprised 36 BBD diagnoses grouped within four broad histologic classes and four additional descriptors retained separately (**Table 1**).

The grouping framework was refined over time through quality control and expert pathologist review, with re-abstraction when necessary, as described below. New questions and regroupings also arose during subsequent data submissions and related research projects, leading to further adjustments. This iterative process ensured that the BBD diagnosis groups were robust, internally consistent, and suitable for precise estimation of associations with cancer risk.

Harmonization Across Registries

Harmonization primarily involved reconciling variability in how registries abstracted or labeled benign diagnoses, including differences in diagnostic specificity and terminology across sites. In some cases, this required targeted re-abstraction when diagnoses were too vague or nonspecific. For example, one registry frequently submitted an “atypical hyperplasia” diagnosis without distinguishing “atypical ductal hyperplasia” from “atypical lobular hyperplasia”. Likewise, some registries had mapped some diagnoses to a general “nonproliferative changes not otherwise specified (NOS)” diagnosis, and this also required re-abstraction to recover more specific diagnoses. Harmonization efforts ensured greater consistency and comparability across sites.

Structured Approach for Nonspecific Diagnoses

To further standardize terminology and address nonspecific pathology terminology, we developed structured diagnostic categories to capture cases that were nonspecific but still clinically interpretable. For example, nonspecific benign diagnoses were classified as epithelial benign, stromal benign, or benign stromal neoplasm, depending on the predominant tissue type, with remaining unclassifiable cases assigned to benign not otherwise specified. Similarly, atypia NOS was created for terms that could not be clearly classified as atypical ductal hyperplasia, atypical lobular hyperplasia, atypical hyperplasia, or papillary with atypia. For fibrocystic changes NOS, the NOS label was reserved for biopsies with a diagnosis recorded simply as “fibrocystic changes” without accompanying features (e.g., “apocrine metaplasia”, “fibrosis”, “cysts”) that would allow assignment to a more specific diagnosis. These fallback categories provided a standardized approach to handling vague or incomplete terminology while minimizing loss of clinical information.

Handling of Multiple Diagnoses

Classification approaches were developed to capture diagnoses with multiple coexisting histologic features. Representative examples included coding “complex sclerosing papillary lesion” as both papilloma and radial scar, while a “sclerosing papillary lesion with atypia” was coded as both papillary with atypia and sclerosis. “Mucocele-like lesions” were coded as both cysts and inflammation.

Expert Pathologist Review and Validation

Two expert breast pathologists (AB, DW) reviewed the classification schema and provided input on the grouping of specific terms. Clinical synonyms (e.g. moderate

epithelial hyperplasia, usual ductal hyperplasia (UDH)) were combined into a single BBD diagnosis. Ambiguities, such as whether “atypical intraductal papillary proliferation” should be classified as atypical ductal hyperplasia or papillary with atypia, were resolved through structured discussions and consensus. A critical component of discussion and arbitration was the review of hazard ratio estimates of breast cancer risk associated with BBD diagnoses to assess whether observed associations aligned with expected clinical outcomes and were consistent with their placement into broad risk categories. Sensitivity analyses evaluated the robustness of groupings by re-categorizing borderline entities (e.g., separating fibroadenomatous hyperplasia from fibroadenoma) and re-estimating breast cancer risk associations. In some instances, terminology did not align intuitively with final classification when hazard ratios for breast cancer risk were considered (e.g. flat epithelial atypia, atypical columnar cell hyperplasia); in these situations, risk determined final classification. Specifically, some BBD diagnoses containing descriptive terms such as “atypia” or “atypical” had hazard ratios more consistent with “proliferative without atypia” than “proliferative with atypia”.

Web-based Application

As a translational component of this framework, we are developing a web-based application to enable practical use of the harmonized BBD classification schema. The application enables users to (1) select a BBD diagnosis to view the pathology terms/descriptors assigned within it; (2) enter a specific pathology term to identify the corresponding standardized BBD diagnosis; and (3) view the broad BBD category (non-proliferative lesions, proliferative changes without atypia, proliferative changes with atypia,

or LCIS) associated with each diagnosis to determine how it aligns with established breast cancer risk strata.

The application provides a single interface for translating heterogeneous pathology terminology into standardized BBD diagnoses. For example, a user may enter a pathology term such as “apocrine hyperplasia,” which maps to the standardized diagnosis of usual ductal hyperplasia (**Figure 2a**), demonstrating how variable terminology is harmonized within the framework. Selecting a standardized diagnosis displays the range of mapped pathology terms (**Figure 2b**), illustrating variation in terminology used by pathologists in clinical practice. The corresponding broad histologic category is also displayed (**Figure 2c**), indicating classification within the proliferative without atypia category. The application also supports entry of multiple pathology terms and returns the highest corresponding broad histologic category based on hierarchical classification rules, with optional display of individual term mappings (**Figure 2d**), providing a summary of the most clinically relevant category when multiple findings are present.

Discussion

We develop a harmonized framework that systematically mapped 624 diverse pathology terms into a structured BBD classification schema comprising 36 BBD diagnoses and 4 descriptors that are clinically meaningful, histologically consistent, and suitable for breast cancer risk analyses. To achieve breast pathology data harmonization, we grouped specific pathological terms into common BBD diagnostic categories, re-

abstracted vague diagnoses, standardized registry-specific terms, and developed structured categories for nonspecific terms. The resulting classification schema preserved clinically meaningful distinctions and enabled valid cross-registry evaluation within the BCSC. BBD diagnoses are nested within the conventional broad classes of non-proliferative lesions, proliferative changes without atypia, proliferative changes with atypia, and LCIS, facilitating comparison with prior literature and integration with existing risk models. We also developed a web-based application built on this framework that has the potential to improve communication, enhance consistency in reporting, and support integration of specific BBD diagnosis into breast cancer risk assessment models.

Although harmonized datasets are widely used in population-based research, few investigators report the detailed decision-making required to reconcile heterogeneous diagnostic language. By documenting the harmonization process, quality control checks, and expert adjudication that shaped our approach, this study adds methodological transparency to an area often less thoroughly described in the literature. An important component of our harmonization framework is the development of standardized BBD diagnostic categories based on pathologist review of diagnostic terminology and incorporation of observed future breast cancer risk. A notable strength of this approach is the linkage of BBD diagnostic terms to observed future risk within a large population-based setting that includes both academic and non-academic practice.

In addition to supporting research applications, the framework may also improve transparency and patient understanding in clinical settings. We developed a prototype web-based Shiny application to help make the harmonized classification schema

accessible and understandable for patients, clinicians, and researchers. Users can search pathology terms, view how they map to standardized BBD diagnoses, and identify the broad BBD categories used in breast cancer risk assessment. The application complements current BCSC risk calculators (52) by clarifying which BBD category should be selected when estimating invasive or advanced breast cancer risk (14, 15). Although the calculators already provide a reference list of diagnoses, our application incorporates a substantially broader set of mapped pathology terms encountered in clinical practice. By addressing these gaps, the application may support more accurate risk estimation and potentially help to facilitate informed decision-making between patients and their healthcare providers.

The harmonization process revealed substantial variability in reporting practices across registries and highlighted challenges created by rare, ambiguous, or evolving diagnostic terms. These observations emphasize the importance of continued collaboration among pathologists, registries, and researchers to maintain alignment with current diagnostic standards and adapt to changes in pathology terminology over time. Greater standardization of pathology terminology within health systems could reduce variability in dictated text, similar to how coordinated efforts in radiology produced the Breast Imaging Reporting and Diagnosis System (BI-RADS). Movement toward a comparable classification system for breast pathology could meaningfully reduce variation in pathology reporting across institutions.

The harmonized framework may be useful in multi-center and longitudinal studies, where differences in diagnostic language can complicate comparisons and limit statistical

power. Uniform definitions of BBD diagnosis enable valid analyses across multiple registries and facilitate integration with risk modeling efforts and population-based datasets. This approach supports large-scale investigations of breast cancer risk and outcomes while maintaining the clinical specificity of specific BBD diagnoses.

While designed to be comprehensive, the harmonized terminology has some potential limitations in that it may not capture all pathology terms used in clinical practice. However, the framework and accompanying application can be updated as new terminology is identified. Continued input from clinicians and pathologists will be important for identifying terms that may be missing or mapped differently than expected. Such ongoing dialogue will help refine and strengthen the classification schema as diagnostic language continues to evolve.

Conclusion

In summary, this work demonstrates the feasibility and value of harmonizing BBD pathology terminology across diverse data sources. The harmonization framework provides a transparent, standardized methodology for reconciling heterogeneous diagnostic language, while the resulting classification schema and companion web application support consistent BBD classification for research and improved accessibility of pathology information for patients and clinicians. This resource provides a durable foundation for future research, progress toward standardized pathology reporting, and effective communication of BBD risk.

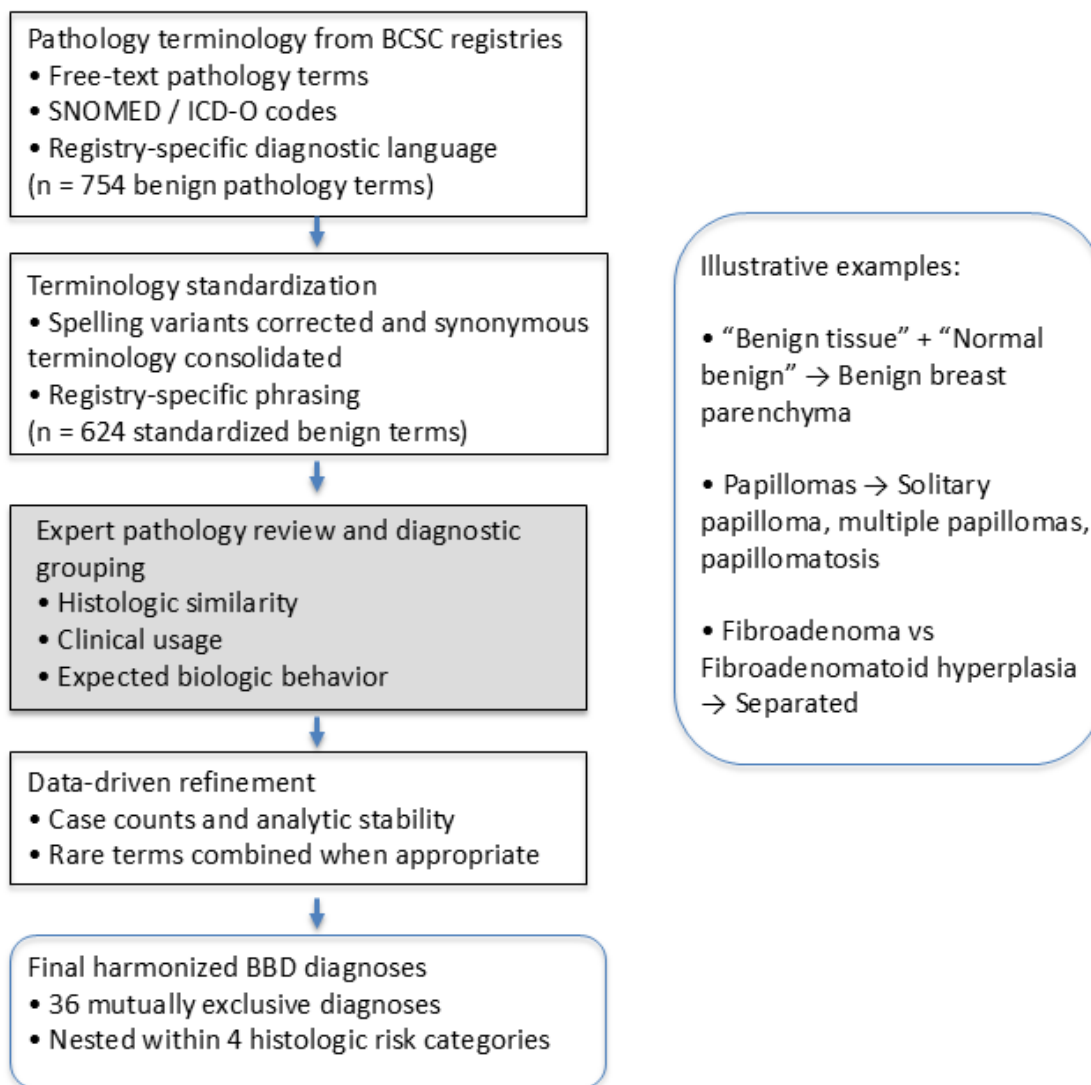


Figure 2.1. Development of the harmonized benign breast disease (BBD) classification.

Pathology terminology from multiple Breast Cancer Surveillance Consortium registries (n=754 unique benign pathology terms) was iteratively standardized to 624 unique terms and mapped into standardized BBD diagnoses through data review, quality control, and expert pathologist consensus. The shaded box denotes the stage at which diagnostic grouping decisions were informed by both expert pathology review and data characteristics. Invasive and in situ carcinoma terms were mapped separately for completeness and integration into the web-based application and are not shown.

Table 2.1. Harmonized benign breast disease classification schema

Broad Histologic Class	Standardized Diagnoses
Lobular carcinoma <i>in situ</i>	Lobular carcinoma <i>in situ</i>
Proliferative changes with Atypia	Atypical lobular hyperplasia; atypical ductal hyperplasia; atypical hyperplasia NOS; atypia NOS; papillary with atypia
Proliferative changes without Atypia	Multiple papillomas; solitary papilloma; flat epithelial atypia; usual ductal hyperplasia; radial scar; columnar cell lesions; papillomatosis
Nonproliferative Lesions	Benign breast parenchyma, fibrocystic changes NOS; benign NOS; adenoma; adenosis; benign stromal neoplasm; pseudoangiomatous stromal hyperplasia; squamous metaplasia; fibroadenoma; adenomyoepithelioma; phyllodes; fibrosis; epithelial benign; sclerosing adenosis; hamartoma; cyst; skin; apocrine metaplasia; stromal benign; fibroadenomatous change/hyperplasia; hemangioma; atrophy
Additional histologic descriptors retained separately from diagnostic categories: calcification, inflammation, sclerosis, granuloma	
Abbreviations: NOS, not otherwise specified	

A.

Pathology term to standardized diagnosis

Pathology Code

apocrine hyperplasia

apocrine hyperplasia maps to UDH

B.

Pathology term to BCSC Risk Calculator Biopsy

Pathology Code

apocrine hyperplasia

apocrine hyperplasia corresponds to Proliferative without atypia.

C.

Pathology term to BCSC Risk Calculator Biopsy

Pathology Code

apocrine hyperplasia calcifications
atypical hyperplasia (adh)

☒ Display individual mappings

Proliferative with atypia is the most severe prior biopsy diagnosis for the following diagnoses: apocrine hyperplasia, calcifications, and atypical hyperplasia (adh).

Show 10 entries

Search:

	Pathology Code	Broad Category
1	apocrine hyperplasia	Proliferative without atypia
2	atypical hyperplasia (adh)	Proliferative with atypia
3	calcifications	Non-proliferative

Showing 1 to 3 of 3 entries

Previous 1 Next

D.

Standardized Diagnosis

UDH

Show 10 entries

Search:

	Pathology Code
1	apocrine hyperplasia
2	bland hyperplasia
3	ductal & lobular hyperplasia
4	ductal epithelial hyperplasia
5	ductal epithelial hyperplasia without atypia
6	ductal hyperplasia
7	ductal hyperplasia (usual type)
8	ductal hyperplasia of the usual type
9	ductal hyperplasia usual
10	ductal hyperplasia without atypia

Showing 1 to 10 of 53 entries

Previous 1 2 3 4 5 6 Next

Figure 2.2. Web-based application for mapping pathology terminology to standardized benign breast disease (BBD) diagnoses.
(A) Entry of a pathology term returns the corresponding standardized diagnosis. (B) The

corresponding broad histologic category is displayed, linking diagnoses to clinically relevant risk groupings. (C) Entry of multiple pathology terms returns the highest corresponding broad histologic category based on hierarchical classification rules, with optional display of individual mappings. (D) Selection of a standardized diagnosis displays the range of mapped pathology terms.

Chapter 3: Ipsilateral and Contralateral Breast Cancer Risk Following Benign Breast Disease

Olivia Sattayapiwat, Brian L. Sprague, Theresa H.M. Keegan, Donald L. Weaver, Alexander D. Borowsky, Karla Kerlikowske, Diana L. Miglioretti

Abstract

Importance: Although proliferative and non-proliferative benign breast disease (BBD) diagnoses are associated with increased breast cancer risk, few studies have evaluated whether future risk of invasive breast cancer and ductal carcinoma in situ (DCIS) following BBD differs by laterality.

Objective: Evaluate whether breast cancer risk following BBD differs between ipsilateral and contralateral breasts by histologic category and time since biopsy.

Design: Breast-level cohort study from 1994 to 2022.

Setting: Breast Cancer Surveillance Consortium registries; United States.

Participants: Women with BBD (127,305 diagnoses in 108,074 women) and a comparison group of 1,599,694 women with no prior breast biopsy and a negative screening mammogram.

Exposures: BBD classified into four histologic categories and categorized as ipsilateral, contralateral, or absent (reference) relative to each breast.

Main Outcomes and Measures: Associations with invasive breast cancer and DCIS were estimated using Fine–Gray competing-risk time-to-event models. Temporal patterns among women with BBD who developed breast cancer were evaluated using relative risks.

Results: All BBD categories were associated with increased risks of invasive cancer and DCIS in both breasts, with strongest associations for lobular carcinoma in situ (LCIS) and weakest for nonproliferative changes. After an LCIS diagnosis, risks of invasive cancer and DCIS were strongly elevated in both the ipsilateral and contralateral breast (invasive hazard

ratio [HR]=6.55 vs. 4.81, $P=0.49$; DCIS HR=10.2 vs. 10.7, $P=0.94$). Proliferative changes with atypia, proliferative changes without atypia, and nonproliferative changes showed stronger ipsilateral than contralateral associations with invasive cancer (HRs=4.84 vs. 3.43, 2.89 vs. 2.16, 2.23 vs. 1.80, respectively; $P=0.04$, 0.01, and $P<0.01$) and DCIS (HRs=8.83 vs. 4.16, 4.55 vs. 3.22, 2.28 vs. 1.84, respectively; $P=0.01$, 0.04, and 0.07). Overall, relative differences in ipsilateral versus contralateral cancer risk were greatest within 10 years of BBD diagnosis (<5 years RR=1.42, 95% CI: 1.33–1.52; 5–10 years RR=1.24, 95% CI: 1.14–1.36) and were not significant thereafter.

Conclusions and relevance: BBD diagnoses were associated with bilateral breast cancer risk, with stronger ipsilateral than contralateral associations for both invasive breast cancer and DCIS, particularly within the first 10 years after biopsy. These results may inform risk stratification, primary prevention, screening strategies, and etiologic models of breast carcinogenesis.

Introduction

Benign breast disease (BBD) is diagnosed in over 75% of breast biopsies performed annually in the US (2), and certain benign diagnoses are associated with increased risk of subsequent breast cancer (3, 4, 36). BBD is typically classified into four broad histologic groups based on degree of epithelial proliferation and atypia: nonproliferative changes (NPC), proliferative changes without atypia (PWoA), proliferative changes with atypia (PWA), and lobular carcinoma in situ (LCIS), with LCIS representing the highest-risk category (5-7).

Whether BBD lesions function as direct precursors to malignancy or alternatively represent markers of an underlying host/tissue environment that predisposes to cancer remains uncertain. Laterality and timing of subsequent breast cancer may provide insight into this distinction (4). Features supporting a precursor role include a greater likelihood of cancers arising in the ipsilateral breast and within a relatively short interval following biopsy, whereas persistent risk over longer follow-up periods, including contralateral events, would be consistent with lesions acting as markers of generalized susceptibility. Evaluating these patterns separately for invasive breast cancer and ductal carcinoma *in situ* (DCIS) by laterality may further inform these distinctions.

Relatively few studies have examined whether subsequent cancers are more likely to arise in the same (ipsilateral) or opposite (contralateral) breast as the original benign lesion. Prior investigations of laterality following BBD have been limited in number and scope and have largely focused on higher-risk lesions, often in studies with relatively

modest sample sizes (25-28), with the largest study including approximately 1,200 breast cancer cases (2).

We evaluated laterality-specific breast cancer risk following BBD in a large, population-based cohort from the Breast Cancer Surveillance Consortium (BCSC) with long-term follow-up. We examined invasive breast cancer and DCIS as distinct outcomes, assessed temporal patterns of ipsilateral and contralateral risk, and evaluated whether associations differed by broad histologic category and selected BBD diagnoses.

Methods

Data Sources

The study cohort was identified from the BCSC, which comprises regional registries from across the United States that link demographic and clinical characteristics to breast imaging data from community and academic radiology facilities, breast biopsy pathology results, and breast cancer outcomes (<https://www.bcsc-research.org>). Eight BCSC registries (Carolina Mammography Registry in North Carolina; Kaiser Permanente Washington Registry; Metro Chicago Breast Cancer Registry; New Hampshire Mammography Network; Sacramento Area Breast Imaging Registry; San Francisco Mammography Registry; Northwest Screening and Cancer Outcomes Research Enterprise; and Vermont Breast Cancer Surveillance System) contributed data for this analysis. Each BCSC registry and the Statistical Coordinating Center received institutional review board

approval for all study procedures, which are Health Insurance Portability and Accountability Act compliant.

At breast imaging exams, women complete a health history questionnaire with questions on demographics; height and weight; risk factors, including family history of breast cancer; clinical history, including history of breast cancer and breast procedures, and menopausal status. These data are supplemented with information from electronic health records. Pathology data collected on benign and malignant breast biopsies and breast surgeries included procedure date, procedure type, laterality, and pathology results.

The primary outcomes for this analysis were invasive breast carcinoma and DCIS. Breast cancer diagnoses and tumor characteristics are obtained through linkage to pathology databases and regional or state cancer registries. Deaths on all women, including those without cancer, are obtained through linkages with state and administrative death records.

Study Population

The study population included women ages 35-79 years from 1994-2022. Among women with a breast biopsy, we excluded biopsies from women with prior breast cancer or mastectomy and biopsies followed by a breast cancer diagnosis within 6 months. Biopsies performed on the same day and breast were combined into a single observation and for each woman, one observation per biopsy per day was created for each breast. Women could contribute multiple pairs of observations if she had benign biopsies on multiple days.

We excluded 6,773 biopsies with unknown BBD laterality, for a final sample of 127,305 biopsy episodes in 108,074 women.

For the comparison group, we selected women with a negative screening mammography assessment (BI-RADS 1 or 2) and no prior breast biopsy, breast cancer diagnosis, or mastectomy at the time of that mammogram, and no breast cancer diagnosed within the following 6 months. Women who later underwent a biopsy were eligible to be controls if they had an eligible mammogram prior to their first biopsy. If multiple eligible mammograms were available for a woman, one was randomly selected, resulting in 1,599,694 in the comparison group.

For women with unilateral BBD, each biopsy contributed two breast-level records, one representing the breast with the benign lesion (ipsilateral) and one representing the opposite breast (contralateral). For women with bilateral BBD, two breast-level records were included, one for each breast, both coded as ipsilateral exposure. In the comparison group, both breasts were included as separate breast-level records per woman, both coded as no BBD. The final analytic dataset included 3,453,998 total breast-level records among 1,663,004 women.

Benign breast disease classification

For each breast, history of BBD was classified into three mutually exclusive categories: (1) BBD in that breast (ipsilateral exposure), (2) BBD in the opposite breast (contralateral exposure), or (3) no history of BBD in either breast. We evaluated four broad BBD categories (LCIS, PWA, PWOA, and NPC) and specific diagnoses within these

categories with at least 10 events to allow stable estimation of associations, including atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), PWA other, usual ductal hyperplasia, papillomas, columnar cell lesions, radial scar, and PWOA other.

Grouped “other” categories with fewer events were retained for completeness.

A hierarchical classification scheme was applied across BBD categories (LCIS > PWA > PWOA > NPC) separately within each breast, such that each observation contributed a single BBD category per breast. Histologic diagnoses were also grouped into high- (LCIS and PWA) and low-risk (PWOA, NPC) categories consistent with prior literature (16, 37-39).

Statistical Analysis

Baseline characteristics of the study population were summarized at the observation level for biopsy episodes with high-risk and low-risk histologic diagnoses and for women with a negative screening mammogram.

Analyses were conducted at the breast level. We evaluated associations between BBD and subsequent breast cancer using partly conditional competing-risk regression models (41) based on the Fine–Gray approach (42), estimating hazard ratios (HRs) and 95% confidence intervals (95% CI). Death, diagnosis of cancer of another type (i.e., DCIS when modeling invasive carcinoma), and cancer occurring in the opposite breast were treated as competing events for the outcome being modeled. The robust sandwich variance estimator and inverse-weighting by the number of observations were used to account for multiple observations from the same woman (43). BCSC registry was included as a stratification

variable. Follow-up started 6 months after each biopsy or screening mammogram to avoid including prevalent breast cancers. Follow-up ended at the earliest of a breast cancer diagnosis, death, end of complete cancer capture, 5 years after the last breast imaging in the BCSC, or 10 years.

Two sets of models were fit to estimate HRs for broad BBD diagnoses (LCIS, PWA, PWoA, and NPC); and 2) specific BBD diagnoses. Within each, separate models were fit for invasive breast carcinoma and DCIS, adjusting for age at biopsy. HRs were estimated for ipsilateral and contralateral breast cancer and differences between ipsilateral and contralateral associations were assessed using Wald tests.

For breast cancer diagnoses with missing laterality (381/73,685=0.52%), laterality was randomly assigned based on the overall distribution of left- versus right-sided cancers in the analytic cohort. To assess the robustness of results to assumptions regarding cancer laterality, sensitivity analyses were conducted in which all cancers with missing laterality were alternatively classified as all ipsilateral or as all contralateral.

Among women who developed breast cancer, we also examined the cancer laterality relative to the BBD within five-year intervals since biopsy (0-5, 5-10, 10-15, 15-20, and >20 years), using an approach similar to Hartmann et al (4). For these analyses, follow-up was extended beyond the 10-year limit used in the main risk models to evaluate longer-term temporal patterns. Follow-up time was censored symmetrically at the time of diagnosis of the opposite-side cancer, resulting in identical person-time for ipsilateral and contralateral outcomes. Relative risks (RRs) were estimated as the ratio of ipsilateral to

contralateral breast cancer events, with exact binomial methods used to estimate RRs and 95% CIs.

All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Results

Compared with the negative mammogram group, women with high-risk and low-risk histologic groups were generally older and had a higher prevalence of dense breasts and first-degree family history of breast cancer, with these characteristics most pronounced in the high-risk BBD group (**Table 1**). Laterality of BBD was evenly distributed between left and right breasts, with fewer than 1% bilateral. Over a median of 7.5 years (IQR=4.5-10 years) of follow-up, 35,044 invasive breast cancers and 9,703 DCIS diagnoses were observed.

Compared with women with negative screening mammograms, women with LCIS had the highest invasive cancer risk (**Table 2**), with elevated HRs in both the ipsilateral (HR=6.55, 95%CI=3.68–11.7) and contralateral breast (HR=4.81, 95%CI=2.47–9.35; $p=0.49$ for difference between ipsilateral and contralateral HRs). For PWA, HRs were significantly higher ($p=0.04$) for ipsilateral (HR=4.84, 95%CI=3.93–5.96) than contralateral (HR=3.43, 95%CI=2.68–4.39) invasive cancer. For PWoA and NPC, associations were more modest but were still significantly higher for ipsilateral (PWoA HR=2.89, 95%CI=2.53–3.30; NPC HR=2.23, 95%CI=2.05–2.41) than contralateral invasive cancer (PWoA HR=2.16,

95%CI=1.86–2.52; $p=0.01$; NPC HR=1.80, 95%CI=1.65–1.97; $p<0.01$). Similar patterns were observed for risk of DCIS (**Table 2**).

Among specific BBD diagnoses, most lesions demonstrated higher HRs for invasive breast cancer in the ipsilateral breast compared with the contralateral breast (**Table 3**). The strongest associations were observed for atypical lesions, including ADH (ipsilateral HR=4.49, 95%CI=3.35–6.03 vs. contralateral HR=3.15, 95%CI=2.22–4.48) and ALH (ipsilateral HR=6.10, 95%CI=4.18–8.90 vs. contralateral HR=4.01, 95%CI=2.52–6.38), although laterality differences were not statistically significant. In comparison, usual ductal hyperplasia demonstrated a significantly higher risk ($p=0.03$) in the ipsilateral breast (HR=2.45, 95%CI=2.06–2.90) than in the contralateral breast (HR=1.84, 95%CI=1.51–2.23). Other diagnoses, including PWA other, papillomas, columnar cell lesion, radial scar, and PWoA other, were associated with moderate to weak elevations in invasive cancer risk, with modest and non-significant differences in HRs between ipsilateral and contralateral breast cancer.

For DCIS, similar patterns were observed (**Table 3**). ADH was most strongly associated with DCIS risk, with stronger associations ($p=0.02$) in the ipsilateral (HR=9.71, 95%CI=6.56–14.36) than contralateral (HR=4.10, 95%CI=2.25–7.46) breast. Elevated risk was also observed for other diagnoses within the proliferative categories (with and without atypia), although laterality differences were generally not statistically significant.

Results were similar in sensitivity analyses that alternatively classified cancers with missing laterality as ipsilateral or contralateral. In broad-category models, the largest

relative change in hazard ratio was 1.7% for both invasive breast cancer and DCIS (data not shown).

With extended follow-up beyond 10 years, a total of 57,893 invasive breast cancers and 14,760 DCIS were observed. Among women with a breast cancer diagnosis (invasive carcinoma or DCIS), cancer was more common in the same (ipsilateral) breast as the BBD (**Figure 1**). Ipsilateral predominance was evident within 10 years of diagnosis, with the strongest associations during within 5 years (RR=1.42, 95%CI=1.33–1.52; 2,100 ipsilateral and 1,474 contralateral events) and attenuation during years 6–10 (RR=1.24, 95%CI=1.14–1.36), with smaller associations and less precision after 10 years. Results were similar when subdividing by invasive carcinoma and DCIS (**Figure 2**).

Discussion

We observed that the risk of invasive breast cancer and DCIS was increased in both breasts following proliferative and nonproliferative BBD diagnoses; however, risk was increased more in the ipsilateral than contralateral breast, particularly within the first 10 years after biopsy. These findings support interpreting BBD as an epithelial precursor or marker of localized breast microenvironmental risk in addition to a generalized increase in risk. When we considered broad BBD histologic categories, LCIS was strongly associated with elevated breast cancer risk in both breasts, whereas PWA, PWOA, and NPC showed more modest associations that were greater in the ipsilateral than contralateral breasts. Our results leverage a large cohort to characterize laterality-specific risk across the full

spectrum of BBD categories, providing more precise and comprehensive estimates of ipsilateral and contralateral invasive breast cancer and DCIS risk beyond the high-risk lesions emphasized in prior studies.

We observed ipsilateral predominance for both invasive breast cancer and DCIS within 10 years after BBD diagnosis, with the strongest differences in the first 5 years consistent with prior work (4). Differences attenuated over time, especially for invasive cancer. Previous studies of breast cancer laterality following BBD have been limited, largely restricted to high-risk lesions in relatively small cohorts (25-28). Early work characterized LCIS as a marker of bilateral breast cancer risk rather than a direct precursor, a finding supported by multiple epidemiologic studies (26, 28, 53), although more recent molecular data suggest that some LCIS lesions may have precursor potential (54-56). In our study, LCIS was associated with the highest risks of both invasive carcinoma and DCIS. Although ipsilateral and contralateral risks did not differ statistically, ipsilateral risk was higher for invasive cancer. This pattern is consistent with the proposed biology, whereby most LCIS may reflect a host risk effect that affects both breasts, whereas a subset may confer local risk through biological potential for progression, similar to DCIS. These results may warrant further investigation into whether subsets of LCIS differ in their potential for localized progression.

Despite the high prevalence of BBD and its well-established association with breast cancer risk (3, 4, 36), it remains unclear whether these lesions function as true epithelial precursors to malignancy or represent histologic manifestations of an underlying structural and cellular tissue microenvironment that confers increased susceptibility to cancer

development. In our longitudinal analyses, proliferative and nonproliferative benign lesions showed a predominance of ipsilateral breast cancer within 10 years after biopsy, strongest in the first 5 years, a pattern consistent with localized influences on early cancer development. At the same time, elevated contralateral risk was also observed for many lesions, suggesting that these diagnoses may reflect both localized processes and broader, generalized bilateral breast cancer susceptibility. This pattern may reflect more rapid progression in the affected breast and a “head start” in disease development relative to the contralateral breast at the time of biopsy. Over longer follow-up, the attenuation of laterality differences suggests that these localized effects diminish, with subsequent risk increasingly reflecting broader bilateral susceptibility.

Although speculative, the observation of a predominantly ipsilateral pattern among NPC suggests that factors beyond epithelial proliferation may contribute to localized cancer risk. Such factors could involve stromal, inflammatory, or microenvironmental alterations within the affected breast that are not captured by conventional histologic classification. These findings raise the possibility that even lesions traditionally considered low-risk may be associated with breast-specific tissue processes that influence early carcinogenesis.

Laterality differences in risk varied for specific BBD diagnoses, with ADH showing a stronger ipsilateral than contralateral association for DCIS and usual ductal hyperplasia showing a significantly stronger ipsilateral association for invasive breast cancer. Epidemiologic evidence regarding atypical lesions has been mixed. Some investigations have interpreted ADH and ALH as precursors to breast cancer, reflected by predominantly

ipsilateral associations (25, 27), whereas others have suggested that these lesions function primarily as markers of generalized susceptibility (57). Prior work also found a higher proportion of ipsilateral cancers, shorter intervals to diagnosis, and a greater likelihood of carcinoma *in situ* following ADH, supporting a precursor role for a subset of atypical lesions (2). One multi-cohort study extended laterality analyses beyond atypical lesions by examining proliferative lesions both with and without atypia, reporting higher risks of subsequent breast cancer in the ipsilateral versus contralateral breast, although the confidence intervals were wide (45). In contrast, the role of usual ductal hyperplasia is less clear. It has been proposed as an intermediate step in ductal carcinogenesis (5, 6), although subsequent immunohistochemical and molecular evidence has raised questions about a linear precursor role (58-61). In this context, the ipsilateral predominance observed here for usual ductal hyperplasia may provide additional insight into its natural history, suggesting a contribution of localized tissue susceptibility, field effects, or stromal influences rather than a strictly linear precursor pathway.

These findings have important implications for risk stratification, primary prevention, surveillance strategies, and etiologic understanding of BBD. Recognition that laterality-specific breast cancer risk differs by histologic category may help refine counseling and follow-up recommendations after benign biopsy, particularly for women with BBD lesions where risk appears more localized. From a research perspective, incorporating laterality into studies of BBD may provide additional insight into the biological pathways linking benign lesions to later invasive breast cancer and DCIS, by characterizing how risk is distributed between the ipsilateral and contralateral breast over

time since diagnosis, information not captured by overall breast cancer risk assessed across both breasts.

Several limitations should be considered. Pathologic diagnoses were based on reports from practicing pathologists across multiple sites without centralized pathology review, which may introduce diagnostic heterogeneity; however, this approach reflects real-world clinical practice and enhances the relevance of our findings to general populations. Cancer laterality was missing for a small subset of cases, although sensitivity analyses addressing this limitation yielded similar results. Differences in ipsilateral predominance should be interpreted cautiously, as statistical precision varied across diagnoses according to their frequency and number of events; emphasis should therefore be placed on estimated associations and confidence intervals rather than p-values alone. Finally, although laterality differences may provide insight into mechanisms linking BBD to subsequent breast cancer, the observational nature of this study limits our ability to distinguish biological processes from surveillance-related differences in cancer detection.

In summary, breast cancer risk following BBD was higher in the ipsilateral than contralateral breast for most diagnoses and varied by BBD category, with variation in the magnitude of laterality differences across diagnoses. Ipsilateral predominance was evident within the first 10 years after biopsy, with the strongest associations in the first 5 years. These findings support a model in which both localized tissue processes and systemic susceptibility contribute to subsequent breast cancer risk. Consideration of laterality may help clarify the pathways linking BBD to breast cancer and inform more nuanced approaches to clinical surveillance and prevention.

Table 3.1. Descriptive characteristics of study cohort (n=1,726,999 observations), 1994 to 2022

Characteristic	Biopsies with high-risk histologic diagnoses ^b n=7,940 (%)	Biopsies with low-risk histologic diagnoses ^b n=119,365 (%)	Negative mammograms n=1,599,694 (%)
Age, years			
35-49	31.8	44.3	47.4
50-59	36.3	29.3	26.9
60-69	21.0	17.5	16.8
70-79	10.9	8.9	8.9
Benign breast disease laterality			
Right	48.3	48.6	N/A
Left	51.1	50.5	N/A
Bilateral	0.6	0.9	N/A
Race/ethnicity			
Asian / Pacific Islander	8.8	8.2	8.1
Black, non-Hispanic	9.1	12.0	13.3
Hispanic	5.0	5.4	5.4
White, non-Hispanic	75.0	72.1	71.1
Other / multiracial	2.1	2.3	2.1
Unknown	4.4	5.0	9.0
Menopausal status			
Pre or perimenopausal	46.1	54.1	53.1
Postmenopausal	53.9	45.9	46.9
1 st degree family history of breast cancer			
No	79.0	82.2	88.0
Yes	21.0	17.8	12.0
Unknown	11.6	13.1	20.6
BI-RADS breast density			
Almost entirely fat	3.7	5.0	8.4
Scattered fibroglandular densities	31.5	34.3	43.3
Heterogenously dense	51.6	47.5	39.4
Extremely dense	13.3	13.2	8.9
Unknown	6.6	7.6	4.8
Body mass index, kg/m ²			
Underweight (<18.5)	1.5	1.8	1.6
Normal (18.5 - 24.9)	41.3	40.2	40.5
Overweight (25.0-29.9)	28.3	27.3	28.5
Obese (≥30)	28.8	30.6	29.3
Unknown	38.9	39.7	49.9
Follow-up time (median) ^a years	6.1 (4.0—9.8)	6.5 (4.2—10.0)	7.6 (4.5—10.0)
Reason for end of follow-up			
Breast cancer diagnosis	10.5	4.7	2.4

Death	2.3	2.3	2.4
End of complete cancer capture	38.8	39.4	24.6
5 years after the last breast imaging in the BCSC	24.8	25.6	34.0
10 years	23.6	27.9	36.6

^aValues are expressed as median (interquartile range [IQR])

^bHigh-risk histologic diagnoses include lobular carcinoma in situ (LCIS) and proliferative changes with atypia; low-risk histologic diagnoses include proliferative changes without atypia and nonproliferative changes.

Percentage is among non-missing except for unknown row.

Observations for the benign breast disease groups were defined by biopsy episodes collapsed by procedure date and laterality; women could contribute more than one observation.

Follow-up time was calculated from cohort entry until censoring, truncated at 10 years.

Table 3.2. Hazard Ratios for Invasive Carcinoma and Ductal Carcinoma In Situ by Broad Benign Breast Disease Category and Laterality

Laterality of breast cancer relative to BBD	Invasive breast cancer				DCIS		
	Number of breasts	Events (n)	HR (95% CI)	p-value ^a	Events (n)	HR (95% CI)	p-value ^a
Negative mammogram	3,199,388	31,391	1.00 (reference)		8,247	1.00 (reference)	
LCIS							
Ipsilateral	740	50	6.55 (3.68, 11.7)	0.49	17	10.2 (4.08, 25.6)	0.94
Contralateral	738	30	4.81 (2.47, 9.35)		17	10.73 (4.39, 26.3)	
PWA							
Ipsilateral	7,249	321	4.84 (3.93, 5.96)	0.04	159	8.83 (6.53, 11.9)	0.01
Contralateral	7,153	218	3.43 (2.68, 4.39)		80	4.16 (2.69, 6.45)	
PWoA							
Ipsilateral	27,662	715	2.89 (2.53, 3.30)	0.01	285	4.55 (3.66, 5.65)	0.04
Contralateral	27,384	527	2.16 (1.86, 2.52)		200	3.22 (2.48, 4.16)	
NPC							
Ipsilateral	92,730	1841	2.23 (2.05, 2.41)	<0.01	522	2.28 (1.95, 2.65)	0.07
Contralateral	90,954	1442	1.80 (1.65, 1.97)		417	1.84 (1.55, 2.19)	

Hazard ratios (HRs) and 95% confidence intervals (CIs) for invasive carcinoma by benign breast disease (BBD) category and laterality. Ipsilateral HRs represent cancer risk in the same breast as the prior biopsy; contralateral HRs represent risk in the opposite breast. Models were adjusted for age and concurrent BBD diagnoses, with death, DCIS, and cancer of the opposite breast treated as competing risks.

^ap-value for difference between ipsilateral and contralateral HRs

NPC nonproliferative changes, PWoA proliferative disease without atypia, PWA proliferative disease with atypia, and LCIS lobular carcinoma in situ.

Table 3.3. Laterality-specific Hazard Ratios for Invasive Breast Carcinoma and Ductal Carcinoma In Situ by Specific Benign Breast Disease Diagnoses

Laterality of breast cancer relative to BBD	Number of breasts	Invasive breast cancer			Events (n)	DCIS	
		Events (n)	HR (95% CI)	p-value ^a		HR (95% CI)	p-value ^a
Negative mammogram	3,199,388	31,391	1.00 (reference)		8247	1.00 (reference)	
ADH							
Ipsilateral	3,752	164	4.49 (3.35, 6.03)	0.13	98	9.71 (6.56, 14.4)	0.02
Contralateral	3,710	113	3.15 (2.22, 4.48)		47	4.10 (2.25, 7.46)	
ALH							
Ipsilateral	1,737	91	6.10 (4.18, 8.90)	0.17	25	5.74 (2.73, 12.1)	0.68
Contralateral	1,707	58	4.01 (2.52, 6.38)		17	4.53 (1.94, 10.6)	
PWA other							
Ipsilateral	1,777	67	4.12 (2.64, 6.43)	0.43	36	8.64 (4.68, 16.0)	0.12
Contralateral	1,753	47	3.14 (1.89, 5.23)		16	3.44 (1.30, 9.13)	
Papillomas (single and multiple)							
Ipsilateral	6,131	171	1.99 (1.48, 2.69)	0.92	119	5.02 (3.28, 7.69)	0.14
Contralateral	6,045	137	1.95 (1.41, 2.69)		61	3.00 (1.75, 5.13)	
Usual ductal hyperplasia							
Ipsilateral	20,804	554	2.45 (2.06, 2.90)	0.03	172	2.51 (1.78, 3.54)	0.54
Contralateral	20,616	403	1.84 (1.51, 2.23)		128	2.14 (1.47, 3.13)	
Columnar cell lesion							
Ipsilateral	2,949	47	1.82 (1.05, 3.15)	0.7	18	2.22 (0.90, 5.49)	0.99
Contralateral	2,943	32	1.53 (0.80, 2.93)		16	2.24 (0.82, 6.15)	
Radial scar							
Ipsilateral	1,474	33	1.61 (0.82, 3.14)	0.61	17	1.78 (0.62, 5.09)	0.99
Contralateral	1,462	22	1.22 (0.52, 2.83)		14	1.76 (0.51, 6.07)	
PWoA other							
Ipsilateral	657	17	1.37 (0.60, 3.15)	0.83	6	1.95 (0.55, 6.95)	0.57
Contralateral	633	14	1.57 (0.65, 3.79)		3	0.96 (0.12, 7.64)	

Hazard ratios (HRs) and 95% confidence intervals (CIs) for invasive carcinoma by benign breast disease (BBD) category and laterality. Ipsilateral HRs represent cancer risk in the same breast as the prior biopsy; contralateral HRs represent risk in the opposite breast. Models were adjusted for age and concurrent BBD diagnoses, with death, DCIS, and cancer of the opposite breast treated as competing risks.

^ap-value for difference between ipsilateral and contralateral HRs

ADH atypical ductal hyperplasia, ALH atypical lobular hyperplasia, PWA proliferative disease with atypia, and PWoA proliferative disease without atypia.

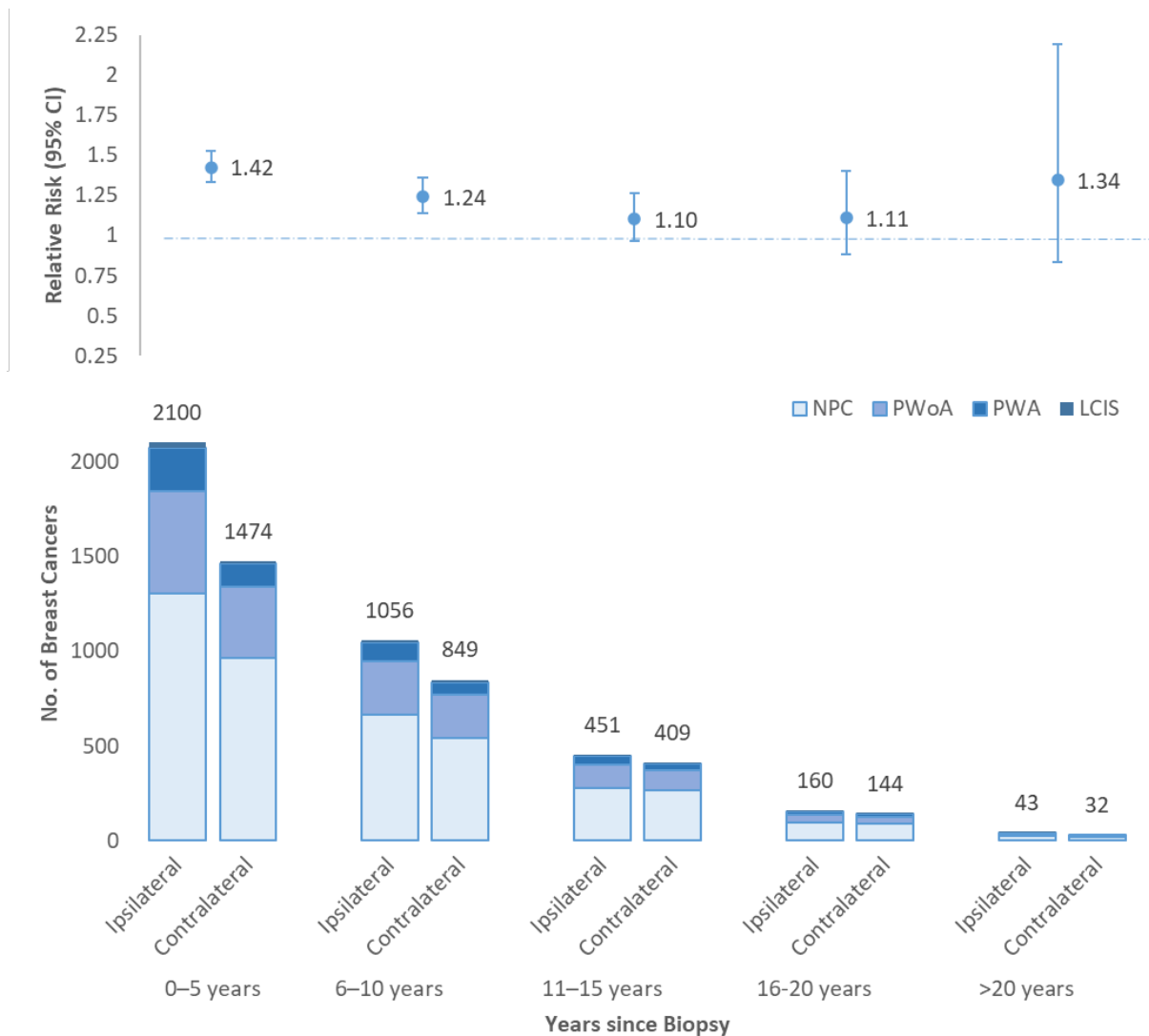


Figure 3.1. Laterality-specific breast cancer diagnoses by time since benign breast disease diagnosis, according to histologic category. Relative risks and 95% confidence intervals comparing ipsilateral with contralateral breast cancer (invasive cancer or DCIS) are shown in the top panel by time since biopsy. The lower panel displays the corresponding numbers of ipsilateral and contralateral breast cancers within each time interval. *CI* denotes confidence interval, *NPC* nonproliferative changes, *PWOA* proliferative disease without atypia, *PWA* proliferative disease with atypia, and *LCIS* lobular carcinoma in situ.

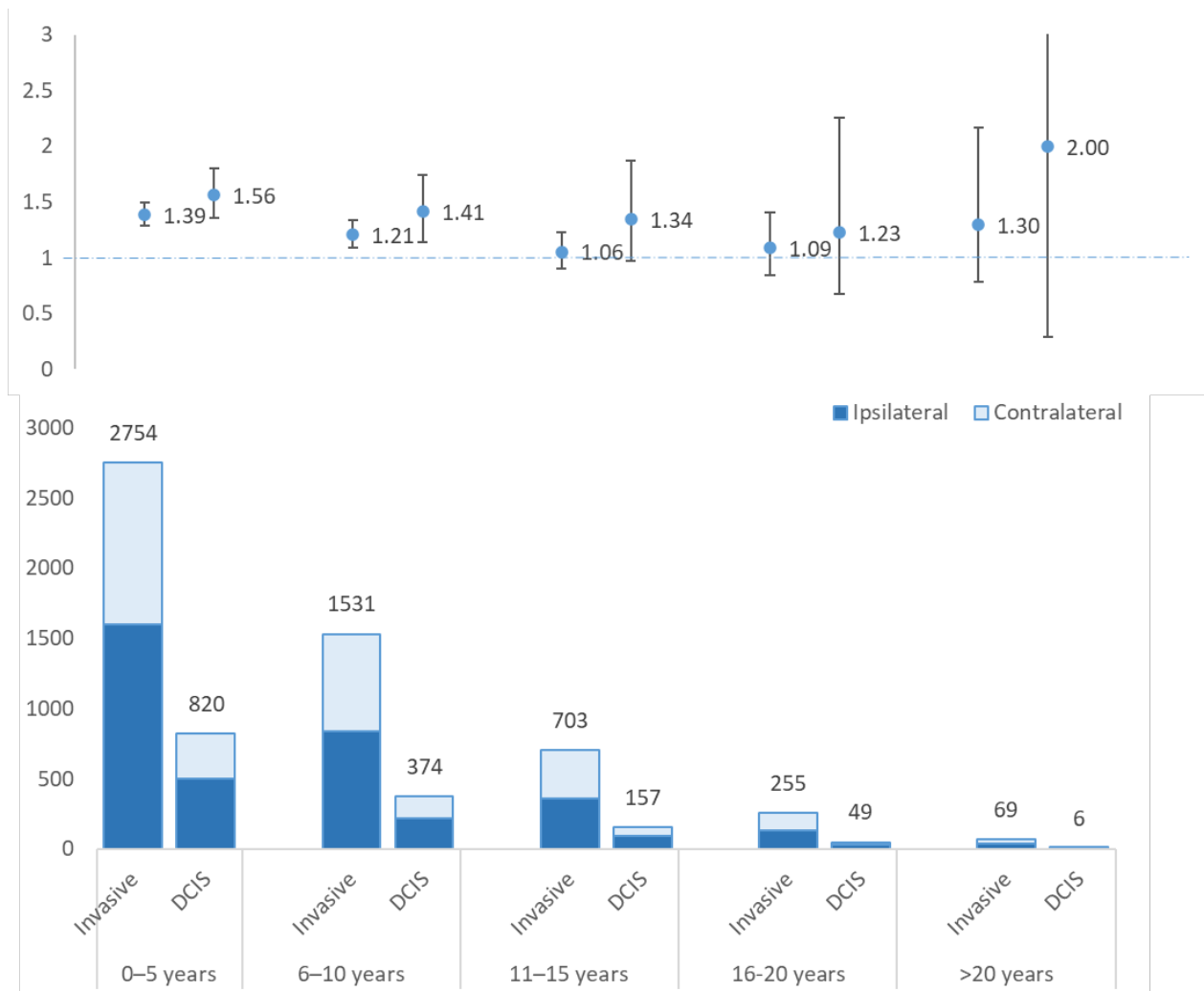


Figure 3.2. Laterality-specific breast cancer diagnoses by time since benign breast disease diagnosis, by cancer type. Relative risks and 95% confidence intervals comparing ipsilateral with contralateral breast cancer are shown in the top panel by time since biopsy separately for invasive breast cancer and ductal carcinoma *in situ* (DCIS). The lower panel displays the corresponding numbers of ipsilateral and contralateral invasive breast cancers and DCIS events within each time interval. Some confidence intervals extend beyond the plotting range at longer durations of follow-up due to small numbers of DCIS events and were truncated. *CI* denotes *confidence interval*.

Conclusion and Public Health Implications

Given the widespread use of breast cancer screening mammography and the frequency of subsequent breast biopsy, benign breast disease (BBD) is a common diagnosis and an established risk factor for future invasive breast cancer. However, the etiology and risk associated with specific BBD diagnoses has been relatively unexplored in the last few decades. Much of the existing literature relies on broad histologic categories, which may obscure important variation in risk across individual diagnoses.

This dissertation builds on prior work from the Breast Cancer Surveillance Consortium by leveraging data from a large, diverse population of women to provide more precise estimates of breast cancer risk across a wide range of BBD diagnoses. These findings demonstrate substantial heterogeneity in risk within conventional categories and highlight the importance of evaluating specific diagnoses rather than relying solely on broad groupings. To support this work, we developed a harmonized classification framework that integrates heterogeneous pathology terminology into standardized BBD diagnoses, enabling more consistent risk assessment, comparison across studies, and potential integration into clinical risk tools. In addition, examination of laterality patterns offers insight into potential biological mechanisms underlying disease progression, suggesting that both localized and systemic processes may contribute to risk.

Together, these results have important implications for improving breast cancer risk prediction and informing clinical management. More refined characterization of risk associated with specific BBD diagnoses may support more individualized screening and prevention strategies, reduce unnecessary imaging for lower-risk lesions, and help identify

women who may benefit from more intensive surveillance or risk-reducing interventions.

Continued efforts to standardize BBD terminology and integrate these findings into clinical risk assessment tools may further enhance their utility in diverse populations.

REFERENCES

1. Silverstein, M., *Where's the outrage?* J Am Coll Surg, 2009. **208**(1): p. 78-9.
2. Visscher, D.W., et al., *Clinicopathologic features of breast cancers that develop in women with previous benign breast disease.* Cancer, 2016. **122**(3): p. 378-85.
3. Gail, M.H., et al., *Projecting individualized probabilities of developing breast cancer for white females who are being examined annually.* J Natl Cancer Inst, 1989. **81**(24): p. 1879-86.
4. Hartmann, L.C., et al., *Benign breast disease and the risk of breast cancer.* N Engl J Med, 2005. **353**(3): p. 229-37.
5. Dupont, W.D. and D.L. Page, *Risk factors for breast cancer in women with proliferative breast disease.* N Engl J Med, 1985. **312**(3): p. 146-51.
6. Page, D.L., et al., *Atypical hyperplastic lesions of the female breast. A long-term follow-up study.* Cancer, 1985. **55**(11): p. 2698-708.
7. Tice, J.A., et al., *Benign breast disease, mammographic breast density, and the risk of breast cancer.* J Natl Cancer Inst, 2013. **105**(14): p. 1043-9.
8. Dupont, W.D., et al., *Breast cancer risk associated with proliferative breast disease and atypical hyperplasia.* Cancer, 1993. **71**(4): p. 1258-65.
9. London, S.J., et al., *A prospective study of benign breast disease and the risk of breast cancer.* Jama, 1992. **267**(7): p. 941-4.
10. Bodian, C.A., et al., *Reproducibility and validity of pathologic classifications of benign breast disease and implications for clinical applications.* Cancer, 1993. **71**(12): p. 3908-13.
11. Carter, C.L., et al., *A prospective study of the development of breast cancer in 16,692 women with benign breast disease.* Am J Epidemiol, 1988. **128**(3): p. 467-77.
12. Dyrstad, S.W., et al., *Breast cancer risk associated with benign breast disease: systematic review and meta-analysis.* Breast Cancer Res Treat, 2015. **149**(3): p. 569-75.
13. Wang, J., et al., *Lower-category benign breast disease and the risk of invasive breast cancer.* J Natl Cancer Inst, 2004. **96**(8): p. 616-20.
14. Gard, C.C., et al., *Extending the Breast Cancer Surveillance Consortium Model of Invasive Breast Cancer.* J Clin Oncol, 2024. **42**(7): p. 779-789.
15. Kerlikowske, K., et al., *Cumulative Advanced Breast Cancer Risk Prediction Model Developed in a Screening Mammography Population.* J Natl Cancer Inst, 2022. **114**(5): p. 676-685.
16. Ashbeck, E.L., et al., *Benign breast biopsy diagnosis and subsequent risk of breast cancer.* Cancer Epidemiol Biomarkers Prev, 2007. **16**(3): p. 467-72.
17. Krieger, N. and R.A. Hiatt, *Risk of breast cancer after benign breast diseases. Variation by histologic type, degree of atypia, age at biopsy, and length of follow-up.* Am J Epidemiol, 1992. **135**(6): p. 619-31.
18. Sherman, M.E., et al., *Benign Breast Disease and Breast Cancer Risk in the Percutaneous Biopsy Era.* JAMA Surg, 2024. **159**(2): p. 193-201.
19. Colditz, G.A. and B. Rosner, *Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study.* Am J Epidemiol, 2000. **152**(10): p. 950-64.
20. Tyrer, J., S.W. Duffy, and J. Cuzick, *A breast cancer prediction model incorporating familial and personal risk factors.* Stat Med, 2004. **23**(7): p. 1111-30.
21. Aroner, S.A., et al., *Radial scars and subsequent breast cancer risk: results from the Nurses' Health Studies.* Breast Cancer Res Treat, 2013. **139**(1): p. 277-85.

22. Nassar, A., et al., *Complex fibroadenoma and breast cancer risk: a Mayo Clinic Benign Breast Disease Cohort Study*. Breast Cancer Res Treat, 2015. **153**(2): p. 397-405.
23. Said, S.M., et al., *Flat epithelial atypia and risk of breast cancer: A Mayo cohort study*. Cancer, 2015. **121**(10): p. 1548-55.
24. Visscher, D.W., et al., *Sclerosing adenosis and risk of breast cancer*. Breast Cancer Res Treat, 2014. **144**(1): p. 205-12.
25. Hartmann, L.C., et al., *Understanding the premalignant potential of atypical hyperplasia through its natural history: a longitudinal cohort study*. Cancer Prev Res (Phila), 2014. **7**(2): p. 211-7.
26. Chuba, P.J., et al., *Bilateral risk for subsequent breast cancer after lobular carcinoma-in-situ: analysis of surveillance, epidemiology, and end results data*. J Clin Oncol, 2005. **23**(24): p. 5534-41.
27. Page, D.L., et al., *Atypical lobular hyperplasia as a unilateral predictor of breast cancer risk: a retrospective cohort study*. Lancet, 2003. **361**(9352): p. 125-9.
28. Wong, S.M., et al., *Population-Based Analysis of Breast Cancer Incidence and Survival Outcomes in Women Diagnosed with Lobular Carcinoma In Situ*. Ann Surg Oncol, 2017. **24**(9): p. 2509-2517.
29. Cole, P., J. Mark Elwood, and S.D. Kaplan, *Incidence rates and risk factors of benign breast neoplasms*. Am J Epidemiol, 1978. **108**(2): p. 112-20.
30. Fleming, N.T., B.K. Armstrong, and H.J. Sheiner, *The comparative epidemiology of benign breast lumps and breast cancer in Western Australia*. Int J Cancer, 1982. **30**(2): p. 147-52.
31. Jick, S.S., A.M. Walker, and H. Jick, *Conjugated estrogens and fibrocystic breast disease*. Am J Epidemiol, 1986. **124**(5): p. 746-51.
32. Friedenreich, C., et al., *Risk factors for benign proliferative breast disease*. Int J Epidemiol, 2000. **29**(4): p. 637-44.
33. Jain, R.K., et al., *Atypical ductal hyperplasia: interobserver and intraobserver variability*. Mod Pathol, 2011. **24**(7): p. 917-23.
34. Sidawy, M.K., et al., *Interobserver variability in the classification of proliferative breast lesions by fine-needle aspiration: results of the Papanicolaou Society of Cytopathology Study*. Diagn Cytopathol, 1998. **18**(2): p. 150-65.
35. Sloane, J.P., et al., *Consistency of histopathological reporting of breast lesions detected by screening: findings of the U.K. National External Quality Assessment (EQA) Scheme*. U. K. National Coordinating Group for Breast Screening Pathology. Eur J Cancer, 1994. **30a**(10): p. 1414-9.
36. Tice, J.A., et al., *Breast Density and Benign Breast Disease: Risk Assessment to Identify Women at High Risk of Breast Cancer*. J Clin Oncol, 2015. **33**(28): p. 3137-43.
37. Rageth, C.J., et al., *Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions)*. Breast Cancer Res Treat, 2019. **174**(2): p. 279-296.
38. Bahl, M., *Management of High-Risk Breast Lesions*. Radiol Clin North Am, 2021. **59**(1): p. 29-40.
39. Sharma, N., L.S. Wilkinson, and S.E. Pinder, *The B3 conundrum-the radiologists' perspective*. Br J Radiol, 2017. **90**(1071): p. 20160595.
40. *2013 ACR BI-RADS Atlas: Breast Imaging Reporting and Data System*. Vol. 5. American College of Radiology.
41. Zheng, Y. and P.J. Heagerty, *Partly conditional survival models for longitudinal data*. Biometrics, 2005. **61**(2): p. 379-91.

42. Fine, J.P. and R.J. Gray, *A Proportional Hazards Model for the Subdistribution of a Competing Risk*. Journal of the American Statistical Association. **94**(446): p. 496–509.
43. Williamson, J.M., et al., *Modeling survival data with informative cluster size*. Stat Med, 2008. **27**(4): p. 543-55.
44. Degnim, A.C., et al., *Changes in breast cancer risk associated with benign breast disease from 1967 to 2013*. JNCI Cancer Spectr, 2025. **9**(1).
45. Kabat, G.C., et al., *A multi-center prospective cohort study of benign breast disease and risk of subsequent breast cancer*. Cancer Causes Control, 2010. **21**(6): p. 821-8.
46. Sprague, B.L., et al., *Cumulative 6-Year Risk of Screen-Detected Ductal Carcinoma In Situ by Screening Frequency*. JAMA Netw Open, 2023. **6**(2): p. e230166.
47. Falk, R.S., et al., *Second events following ductal carcinoma in situ of the breast: a register-based cohort study*. Breast Cancer Res Treat, 2011. **129**(3): p. 929-38.
48. Innos, K. and P.L. Horn-Ross, *Risk of second primary breast cancers among women with ductal carcinoma in situ of the breast*. Breast Cancer Res Treat, 2008. **111**(3): p. 531-40.
49. Dupont, W.D. and D.L. Page, *Relative risk of breast cancer varies with time since diagnosis of atypical hyperplasia*. Hum Pathol, 1989. **20**(8): p. 723-5.
50. Román, M., et al., *Long-Term Risk of Breast Cancer after Diagnosis of Benign Breast Disease by Screening Mammography*. Int J Environ Res Public Health, 2022. **19**(5).
51. Henrot, P., et al., *Breast microcalcifications: the lesions in anatomical pathology*. Diagn Interv Imaging, 2014. **95**(2): p. 141-52.
52. *Breast Cancer Surveillance Consortium: BCSC Tools*. Available from: <https://www.bcscresearch.org/tools>.
53. Frykberg, E.R., *Lobular Carcinoma In Situ of the Breast*. Breast J, 1999. **5**(5): p. 296-303.
54. Begg, C.B., et al., *Clonal relationships between lobular carcinoma in situ and other breast malignancies*. Breast Cancer Res, 2016. **18**(1): p. 66.
55. Buerger, H., et al., *Genetic relation of lobular carcinoma in situ, ductal carcinoma in situ, and associated invasive carcinoma of the breast*. Mol Pathol, 2000. **53**(3): p. 118-21.
56. Hwang, E.S., et al., *Clonality of lobular carcinoma in situ and synchronous invasive lobular carcinoma*. Cancer, 2004. **100**(12): p. 2562-72.
57. Collins, L.C., et al., *Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia: results from the Nurses' Health Study*. Cancer, 2007. **109**(2): p. 180-7.
58. Boecker, W., et al., *Usual ductal hyperplasia of the breast is a committed stem (progenitor) cell lesion distinct from atypical ductal hyperplasia and ductal carcinoma in situ*. J Pathol, 2002. **198**(4): p. 458-67.
59. Kusama, R., et al., *Clinicopathological characteristics of atypical cystic duct (ACD) of the breast: assessment of ACD as a precancerous lesion*. Pathol Int, 2000. **50**(10): p. 793-800.
60. Otterbach, F., et al., *Cytokeratin 5/6 immunohistochemistry assists the differential diagnosis of atypical proliferations of the breast*. Histopathology, 2000. **37**(3): p. 232-40.
61. Bombonati, A. and D.C. Sgroi, *The molecular pathology of breast cancer progression*. J Pathol, 2011. **223**(2): p. 307-17.