

Increased Risk of Developing Breast Cancer after a False-Positive Screening Mammogram

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Abstract

Background: Women with a history of a false-positive mammogram result may be at increased risk of developing subsequent breast cancer.

Methods: Using 1994 to 2009 Breast Cancer Surveillance Consortium data, we included women ages 40 to 74 years with a screening mammogram that resulted in a false-positive with recommendation for additional imaging, false-positive with recommendation for biopsy, or true-negative with no cancer within one year following the examination. We used partly conditional Cox proportional hazards survival models to assess the association between a false-positive mammogram result and subsequent breast cancer, adjusting for potential confounders. Adjusted survival curves stratified by breast density and false-positive result were used to evaluate changes in risk over time.

Results: During 12,022,560 person-years of follow-up, 48,735 cancers were diagnosed. Compared with women with a true-

negative examination, women with a false-positive with additional imaging recommendation had increased risk of developing breast cancer [adjusted HR (aHR) = 1.39; 95% confidence interval (CI), 1.35–1.44] as did women with a false-positive with a biopsy recommendation (aHR = 1.76; 95% CI, 1.65–1.88). Results stratifying by breast density were similar to overall results except among women with almost entirely fatty breasts in which aHRs were similar for both the false-positive groups. Women with a false-positive result had persistently increased risk of developing breast cancer 10 years after the false-positive examination.

Conclusion/Impact: Women with a history of a false-positive screening mammogram or biopsy recommendation were at increased risk of developing breast cancer for at least a decade, suggesting that prior false-positive screening may be useful in risk prediction models. *Cancer Epidemiol Biomarkers Prev*; 24(12); 1882–9. ©2015 AACR.

Introduction

In the United States, an estimated 67% of women ages 40 and older undergo screening mammography every 1 to 2 years (1). Among these screening examinations, approximately 16% of first and 10% of subsequent mammograms will generate a false-positive result (2). Over the course of 10 screening mammograms, the estimated cumulative probability of at least one false-positive result is 61% for women screened annually and 42% for women screening biennially (2).

Prior studies examining the risk of breast cancer among women with a history of a false-positive screening mammogram report conflicting findings (3–8). The majority of these studies were conducted in Europe where false-positive rates are substantially lower than in the United States (9, 10). The one study conducted in the United States found that a false-positive result was predic-

tive of future breast cancer risk among postmenopausal but not premenopausal women (6). Although breast density is a strong risk factor for breast cancer and is also associated with elevated false-positive rates (11), no previous study has examined whether a false-positive result influences the risk of developing breast cancer differently for those with nondense versus dense breasts. Given that false-positives are common in the United States, the attributable risk associated with false-positive examinations could be substantial if the association with breast cancer is strong.

Our study sought to extend current knowledge by examining whether the relationship between history of a false-positive screening mammogram result and the risk of developing breast cancer varies according to the type of recommendation associated with false-positive results or by mammographic breast density. Using data from the Breast Cancer Surveillance Consortium (BCSC) from 1994 to 2009 from seven registries, we evaluated the association between false-positive mammograms with differing follow-up recommendations (either workup with imaging alone or workup involving biopsy) and breast cancer risk overall and stratified by breast density. We hypothesized that there would be a greater increase in breast cancer risk among women with a history of false-positive biopsy recommendation results compared with those with a false-positive additional imaging recommendation and that this association would be independent of breast density.

Materials and Methods

Data sources

We utilized data from the BCSC, which are representative of the U.S. population (12). Specifically, we included data from seven

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registries located in New Hampshire, North Carolina, San Francisco Bay Area, Western Washington state, New Mexico, Colorado, and Vermont. Details on the BCSC have been described previously (13). Briefly, at each registry prospective data collection includes self-reported demographic characteristics, indication for mammogram, breast cancer risk factors, Breast Imaging Reporting and Data Systems (BI-RADS) mammography assessment, and breast density (14), and the radiologists' management recommendations. The patient and mammography data are linked with pathology databases and state cancer registry data to obtain information on subsequent cancer diagnoses. Data from each registry are sent to a central Statistical Coordinating Center for quality control and pooled analyses. Each registry and the Statistical Coordinating Center received institutional review board approval for either active or passive consent or a waiver of consent to enroll participants, link study data, and perform analytic studies. All procedures are Health Insurance Portability and Accountability Act compliant and all registries as well as the Statistical Coordinating Center have received a Federal Certificate of Confidentiality.

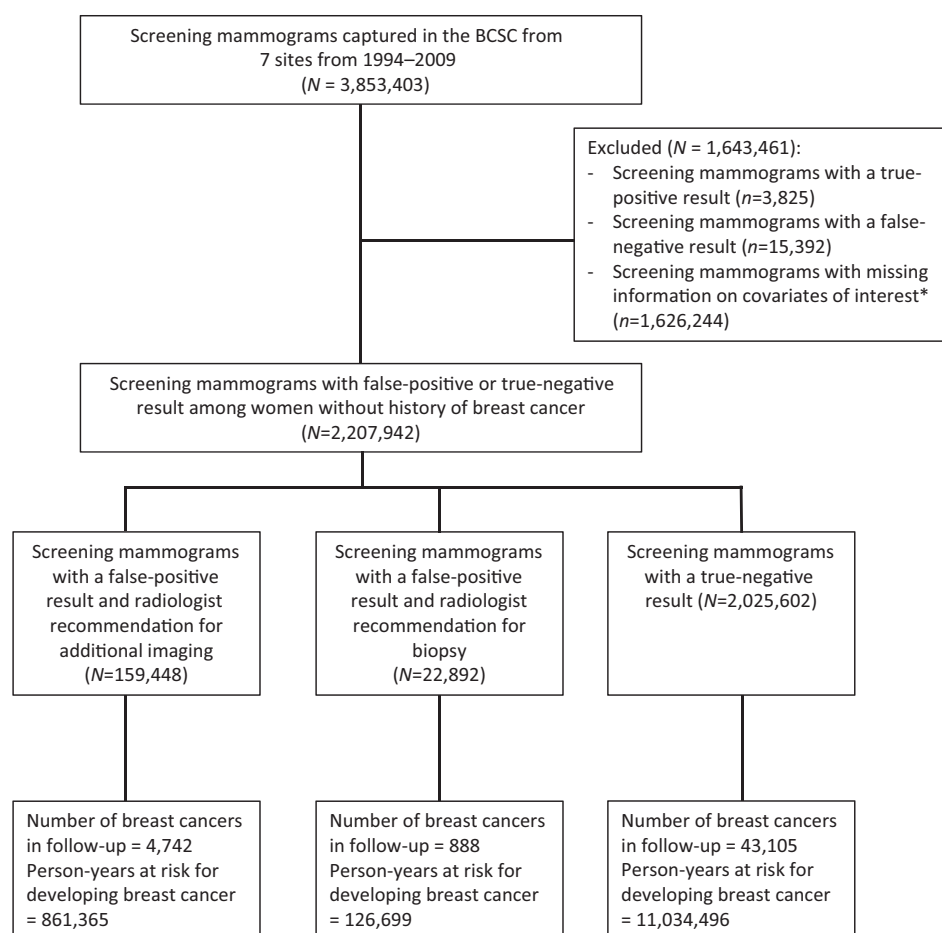
Study population

We included screening mammograms received by women ages 40 to 74 years performed between 1994 and 2009. We excluded women with a prior breast cancer diagnosis and women who lacked complete information on age, race/ethnicity, family history of breast cancer, history of breast biopsy, or BI-RADS breast density. From pathology and cancer registry data we classified women as having incident breast cancer if a diagnosis of invasive carcinoma or ductal carcinoma *in situ* occurred (Fig. 1).

Measures and definitions

At each mammography examination, women completed a questionnaire on demographic and breast health history. Women self-reported race and ethnicity and were categorized as non-Hispanic white, non-Hispanic black, Hispanic, Asian/Native Hawaiian/Pacific Islander, Native American/Native Alaskan, or other. Women were categorized as having a family history of breast cancer if they had at least one first-degree relative with the disease, irrespective of the age of the relative at the time of diagnosis. The time since prior mammography was determined

Figure 1.
Flowchart of study population.



*Covariates with percent missing in parentheses include: age (0%), race/ethnicity (8%), history of breast biopsy (7%), family history of breast cancer (12%), previous mammogram interval (13%), menopause status (25%), and BI-RADS breast density (23%).

10 years of follow-up, or the end of the study period. All models were adjusted for age, race/ethnicity, menopausal status, breast density, history of breast biopsy, time since prior mammogram, and family history of breast cancer. We investigated models with three levels of interaction between density and false-positive mammography results. First, we included only main effects of density and false-positive results without interaction terms. This model assumed that the association between false-positive results and survival was the same for all densities. Next, we added the interaction between false-positive results and breast density to investigate possible differential effects of false-positive results for women with different breast densities. Finally, we fit a model with baseline hazards stratified by breast density and false-positive results to investigate possible time-varying relationships between false-positive groups for each breast density group. Hence, adjusted HR and 95% confidence intervals (CI) for false-positive results are reported (1) overall and (2) separately by breast density based on the interaction model. Results of models with stratified baseline hazards based on density and false-positive results are presented graphically, with follow-up beginning at 12 months after the screening mammogram, in the form of adjusted survival curves as no single HR represents the effect of false-positive results for these models. The proportional hazards assumption was assessed by testing for a statistically significant interaction between the covariate and log time. This test found no evidence of violation of the proportional hazards assumption.

All analyses were conducted using the R version 2.15.3 (R Foundation for Statistical Computing).

Results

The study population included 2,207,942 screening mammograms performed in 1,297,906 women. The highest proportion of

false-positive examinations with recommendations for additional imaging or biopsy occurred among women ages 40 to 49 years (34.8% and 33.1%, respectively; Table 1). False-positive results were also common among premenopausal women. A higher proportion of false-positive examinations were present among women with heterogeneously or extremely dense breasts compared with women with almost entirely fat breasts or scattered fibroglandular densities.

For those with a true-negative result, the total P-Y at risk for developing a breast cancer after the screening examination was 11,034,496 P-Y with a total of 43,105 breast cancers occurring during this time period (Table 2), giving a breast cancer rate per 1,000 P-Y of 3.91 (95% CI, 3.87–3.94). Among those false-positives with imaging recommendation, the breast cancer rate per 1,000 P-Y was 5.51 (95% CI, 5.35–5.66). In false-positives with a biopsy recommendation, the breast cancer rate per 1,000 P-Y was 7.01 (95% CI, 6.56–7.48). Breast cancer rates stratified by BI-RADS breast density showed similar patterns with cancer rates highest for false-positives with a biopsy recommendation and lowest for those with true-negative results for women with scattered fibroglandular densities, heterogeneously dense, or extremely dense breasts. In the almost entirely fat group, the breast cancer rates were similar regardless of false-positive recommendation type (3.69 with 95% CI, 3.07–4.41, for false-positive with an imaging recommendation versus 3.98 with 95% CI, 2.53–5.97, for false-positives with a biopsy recommendation).

During one year of follow-up, 19.2% of women with a false-positive result and 21.0% of women with a true-negative result received a subsequent screening mammogram. The proportion with a screening mammogram in the two groups are similar at 2, 3, 4, and 5 years of follow-up indicating that women with a false-positive are not more likely to be screened in the future compared with women with a true-negative.

Table 1. Characteristics of the study population by screening mammogram result, BCSC

Characteristic	Mammogram classification		
	FP, additional imaging, N = 159,448 N (%)	FP, biopsy, N = 22,892 N (%)	True-negative, N = 2,025,602 N (%)
Age, years			
40–49	55,505 (34.8)	7,577 (33.1)	531,206 (26.2)
50–59	51,227 (32.1)	7,417 (32.4)	661,656 (32.7)
60–69	39,496 (24.8)	5,909 (25.8)	605,282 (29.9)
70–74	13,220 (8.3)	1,989 (8.7)	227,458 (11.2)
Race/ethnicity			
White	137,051 (86.0)	19,063 (83.3)	1,680,964 (83.0)
Black	6,646 (4.2)	1,413 (6.2)	108,256 (5.3)
Asian, Native Hawaiian, Pacific Islander	5,005 (3.1)	876 (3.8)	86,173 (4.3)
Hispanic	9,946 (6.2)	1,405 (6.1)	138,578 (6.8)
American Indian/Alaska Native	800 (0.5)	135 (0.6)	11,631 (0.6)
Menopausal status			
Pre/Peri	63,111 (39.6)	8,749 (38.2)	605,266 (29.9)
Post	96,337 (60.4)	14,143 (61.8)	1,420,336 (70.1)
Family history of breast cancer			
Yes	25,021 (15.7)	3,678 (16.1)	311,419 (15.4)
No	134,427 (84.3)	19,214 (83.9)	1,714,183 (84.6)
History of breast biopsy			
Yes	38,970 (24.2)	6,675 (29.2)	425,906 (21.0)
No	120,478 (75.6)	16,217 (70.8)	1,599,696 (79.0)
BI-RADS breast density			
Almost entirely fat	7,004 (4.4)	1,193 (5.2)	197,148 (9.7)
Scattered fibroglandular densities	65,367 (41.0)	9,331 (40.8)	919,377 (45.4)
Heterogeneously dense	73,470 (46.1)	10,303 (45.0)	754,879 (37.3)
Extremely dense	13,607 (8.5)	2,065 (9.0)	154,198 (7.6)

Abbreviation: FP, false-positive.

Henderson et al.

Table 2. Breast cancer rate per 1,000 P-Y by screening mammogram result and breast density, BCSC

Prior mammogram Result/recommendation	Number breast cancer cases	P-Y at risk	Breast cancer rate (95% CI) per 1,000 P-Y
All women			
True-negative	43,105	11,034,496	3.91 (3.87–3.94)
False-positive, additional imaging	4,742	861,365	5.51 (5.35–5.66)
False-positive, biopsy	888	126,699	7.01 (6.56–7.48)
By BI-RADS breast density			
Almost entirely fat			
True-negative	2,206	993,559	2.22 (2.13–2.31)
False-positive, additional imaging	123	33,291	3.69 (3.07–4.41)
False-positive, biopsy	23	5,774	3.98 (2.53–5.97)
Scattered fibroglandular density			
True-negative	17,884	5,070,911	3.53 (3.37–3.47)
False-positive, additional imaging	1,737	355,192	4.89 (4.51–4.95)
False-positive, biopsy	315	52,612	5.99 (5.09–6.36)
Heterogeneously dense			
True-negative	19,014	4,143,830	4.59 (4.52–4.65)
False-positive, additional imaging	2,372	398,280	5.96 (5.72–6.20)
False-positive, biopsy	448	56,984	7.86 (7.15–8.62)
Extremely dense			
True-negative	4,001	826,197	4.84 (4.69–4.99)
False-positive, additional imaging	510	74,602	6.84 (6.26–7.45)
False-positive, biopsy	102	11,329	9.00 (7.35–10.92)

In Cox proportional hazards models adjusted for age, race/ethnicity, history of benign breast biopsy, time since prior mammogram, and family history of breast cancer, the comparison of those with a false-positive result to those with a true-negative result are shown in Table 3, overall and allowing for an interaction between breast density and false-positive results. The adjusted HR for women with a screening mammogram with a false-positive result with an imaging recommendation was 1.39 relative to women with a true-negative result. Among women with a screening mammogram with a false-positive result with a biopsy recommendation, the adjusted HR was 1.76 relative to women with a true-negative result. In those women with almost entirely fatty breasts, the adjusted HR comparing those with a false-positive imaging recommendation to those with a true-negative result is 1.70 and comparing those with a false-positive biopsy recommendation to those with a true-negative result is 1.77. Among those with scattered fibroglandular densities, heterogeneously dense, and extremely dense breasts, having a false-positive imaging recommendation had an increased HR of 34% to 44% and having a false-positive biopsy recommendation had 74% to 87% higher HR (all *P* values of <0.01).

To determine if the increased risk of developing breast cancer among those with a false-positive result changed over time, we examined survival curves stratified by breast density and false-positive results (Fig. 3). In Fig. 3, the follow-up time begins 12 months after the index mammogram. Among women with almost entirely fat breasts (Fig. 3A), the probability of remaining

breast cancer free for women with a true-negative result at 60 months is 99% compared with 98% for both of the false-positive groups. Both of the false-positive groups appear to have similar survival based on Fig. 3A indicating a similar risk of developing breast cancer and a risk that continues to be slightly higher than that of the true-negative group as far out as 120 months (10 years). For those with scattered fibroglandular densities, the survival plot (Fig. 3B) shows a similar risk for the two false-positive groups up to 24 months and then these two groups begin to diverge with the false-positive biopsy recommendation having the higher risk of developing breast cancer. For those with heterogeneously dense breasts, the risk of developing breast cancer among the false-positive groups diverge after 24 months and there is an increased risk as evidenced by the steeper lines (Fig. 3C). Among those with extremely dense breasts, the risk of developing breast cancer differs among the three groups at 12 months and continues to diverge over time (Fig. 3D).

Discussion

We found that women with a history of a false-positive screening mammogram result were at increased risk of developing breast cancer with those recommended for additional imaging having a 39% higher hazard and those recommended for biopsy having a 76% higher hazard compared with women with a true-negative mammogram result. Stratification by breast density revealed similar results for women with scattered fibroglandular,

Table 3. Adjusted HR from Cox proportional hazards models for screening mammogram result, overall and stratified by breast density groups

Prior mammogram result, recommendation	Overall aHR (95% CI) ^a	BI-RADS breast density			
		Almost entirely fat aHR (95% CI) ^b	Scattered fibroglandular aHR (95% CI) ^b	Heterogeneously dense aHR (95% CI) ^b	Extremely dense aHR (95% CI) ^b
True-negative	Ref.	Ref.	Ref.	Ref.	Ref.
False-positive, additional imaging	1.39 (1.35–1.44)	1.70 (1.42–2.04)	1.44 (1.37–1.52)	1.34 (1.28–1.40)	1.44 (1.31–1.58)
False-positive, biopsy	1.76 (1.65–1.88)	1.76 (1.17–2.66)	1.75 (1.56–1.95)	1.74 (1.59–1.91)	1.87 (1.53–2.27)

^aaHR is adjusted HR with adjustment for age, race/ethnicity, history of breast biopsy, family history of breast cancer, previous mammogram interval, menopause status, and stratified by BI-RADS breast density.

^baHR is adjusted HR for age, race/ethnicity, history of breast biopsy, family history of breast cancer, previous mammogram interval, and menopause status.

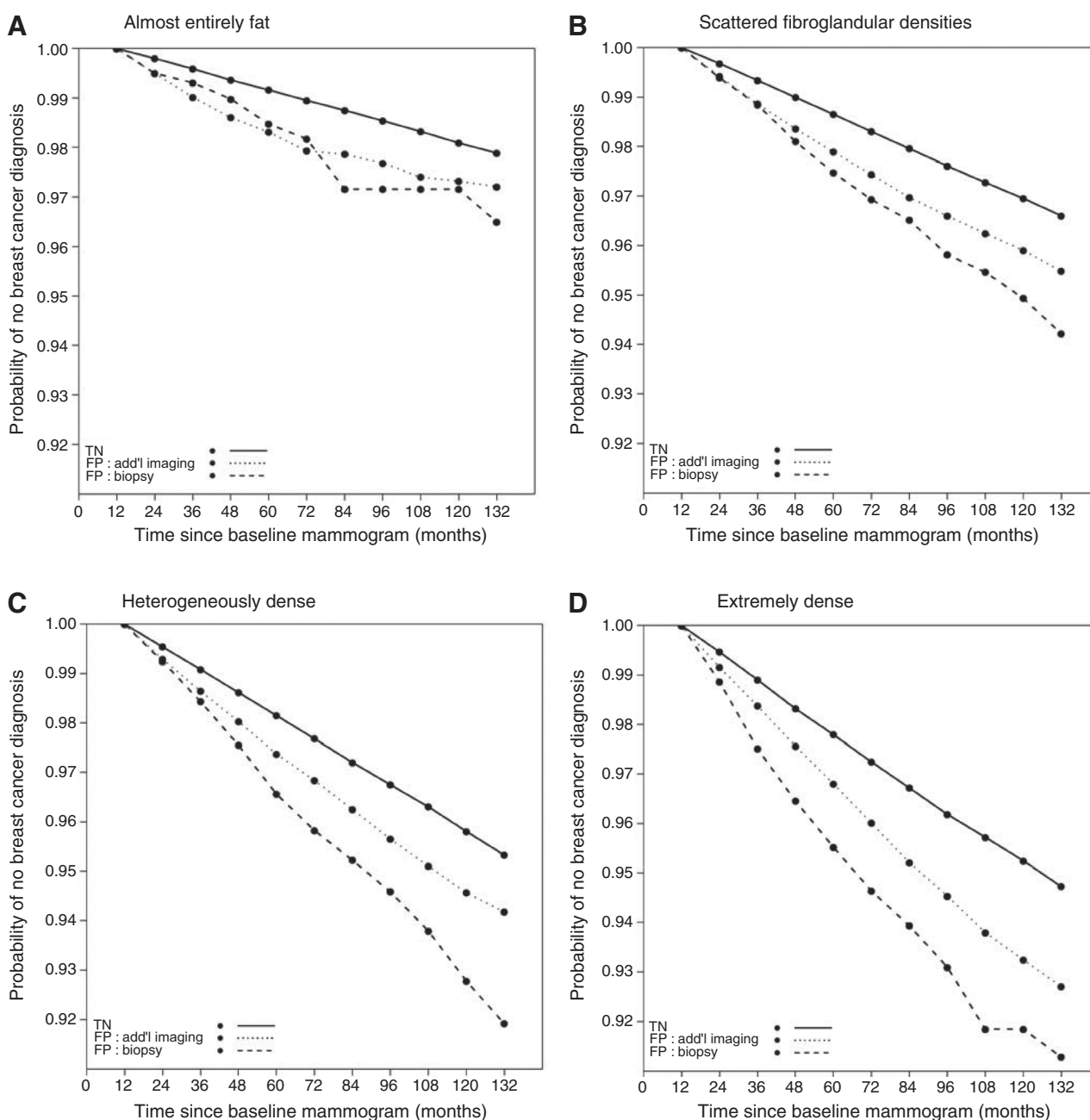


Figure 3.

Adjusted survival curves for breast cancer based on Cox proportional hazards model with baseline hazards stratified by breast density and screening mammogram result. Models are adjusted for age, race/ethnicity, menopausal status, history of breast biopsy, and family history of breast cancer. Solid black line represents true-negative screening mammogram result group; dotted black line represents false-positive with additional imaging recommendation group; dashed black line represents false-positive with biopsy recommendation group. Each breast density group is represented in A–D, where A, almost entirely fat; B, scattered fibroglandular densities; C, heterogeneously dense; and D, extremely dense.

heterogeneously dense, and extremely dense breast tissue; however, among women with almost entirely fatty breasts, both the false-positive groups had about a 70% higher hazard compared to women with a true-negative mammogram result. We also found that women with a history of a false-positive result continued to have an increased risk of developing breast cancer 10 years after experiencing the false-positive result.

Our findings are consistent with several studies. A 2012 study from Denmark examined the long-term risk of breast cancer and found a 67% increased risk among women with a prior false-positive result (7). More recently, data from a population-based breast cancer screening program in Spain reported that false-positive results involving fine needle aspiration cytology or a biopsy had a higher subsequent cancer detection risk than those

Henderson et al.

false-positive results involving additional imaging procedures alone (8). A study from the United Kingdom found that women with a false-positive result on their first screening mammogram had a higher interval cancer rate than women with true-negative results (5). Barlow's BCSC paper from 2006 (6) included prior false-positive mammogram in one-year risk models and found that in multivariate models, prior false-positive was associated with increased risk for postmenopausal, but not premenopausal women. However, Barlow and colleagues used strict criteria ($P < 0.0001$) for determining which patient factors to include in the breast cancer risk prediction model, and in the premenopausal model, the variable indicating the result of the previous mammogram had a P value of 0.0018 (6). We examined our results stratified by menopausal status and found that the HR for the false-positive recommendations were similar by menopausal status [comparing false-positive with additional imaging to true negative for premenopausal HR = 1.32 (95% CI, 1.25–1.39) versus for postmenopausal HR = 1.43 (95% CI, 1.38–1.48); comparing false positive with biopsy to true-negative for premenopausal HR = 1.69 (95% CI, 1.49–1.91) versus for postmenopausal HR = 1.78 (95% CI, 1.64–1.92)]. In contrast with other studies (5–8), two small studies from the Netherlands reported no excess breast cancer risk among women with a prior false-positive compared with women with no history of a false-positive (3, 4).

No prior studies assessed differences in breast cancer risk among women with a false-positive result stratified by breast density. The increase in risk we observed among women with false-positive imaging and biopsy recommendations was similar across density groups, with the exception of the almost entirely fat group. Notably, the absolute risk of breast cancer is higher for women with dense breast tissue. Thus, the highest risk of breast cancer observed in our study was among women with extremely dense breasts who had false-positive results with a biopsy recommendation. Among women with fatty breasts, the absolute risk of breast cancer remained relatively low for both type of false-positive groups.

Our finding that breast cancer risk remains elevated up to 10 years after the false-positive result suggests that the radiologist observed suspicious findings on mammograms that are a marker of future cancer risk. Given that the initial result is a false-positive, it is possible that the abnormal pattern although noncancerous, is a radiographic marker associated with subsequent cancer. About 30% of benign breast biopsies are found to have proliferative changes with or without atypia (16). Thus, these proliferative changes could account, in part, for the increased risk associated with false-positive results with a recommendation for biopsy.

We investigated the possibility of ascertainment bias using the BCSC data to compute the proportion of women in each group (true-negative and false-positive) who received subsequent screening mammograms. Although this does not provide the actual rate of screening because some women may have undergone mammography outside BCSC catchment areas, we can compare the proportions between groups to see if women with false-positives obtained more screening within in the BCSC than true-negatives. Given that the proportion of women with a screening mammogram in the true-negative and false-positive groups is similar, we find no evidence of differential ascertainment of cancer due to more frequent screening.

The current BCSC breast cancer risk prediction model includes age, race/ethnicity, first-degree relatives with breast

cancer, history of breast biopsy, and BI-RADS breast density (17). This model is well calibrated in major race and ethnic groups in the United States and has modest discriminatory accuracy to discern between women who will and will not develop breast cancer (concordance index = 0.66). Given that the survival curves show persistent increases in risk over time and the fact that the increased risk associated with history of a false-positive is independent of breast density and history of breast biopsy, the inclusion of a prior false-positive results may improve risk prediction in the BCSC model.

Strengths of our study include the large sample size, prospective observation, and the ability to follow women for an average of 5.4 years for cancer outcomes. We also were able to include multiple mammography results per woman over time, which increased the statistical power to detect differences by density category. The study population is racially and geographically diverse, with the majority of the examinations coming from community practice. Breast density was assessed using the BI-RADS classification and could be misclassified given the modest inter-rater agreement known to exist, but this is unlikely to affect the results given the similar HR for density categories (18, 19).

Our study also has several limitations. Women may have moved out of our study catchment area and thus we may miss some breast cancer diagnoses; however, we do not expect that this potential loss to follow-up would differ for women with a false-positive versus true-negative result. In addition, we excluded women with missing covariates, which could bias our findings if missingness was not at random. We believe missing values are unrelated to patient or mammogram characteristics because missing values most often arose because a mammography facility did not collect the covariate information during the time when a woman received her mammogram. Since these missing values arose structurally, they are not expected to be associated with patient characteristics and thus will not introduce bias. Another limitation is that data on laterality of the mammographic lesion were not available and thus we are unable to assess how many cancers developed at the site of the initial mammographic lesion and how many were missed cancers.

In conclusion, women with a false-positive screening mammogram result are at increased risk for developing breast cancer, with a higher risk for false-positives with a recommendation for biopsy compared with additional imaging recommendation. The risk was independent of breast density and remained elevated for a decade after receipt of the false-positive result. This information should be considered for inclusion in risk prediction models to better stratify women into risk categories that may be used to personalize breast cancer screening and primary prevention strategies for individual women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NCI or the NIH.

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