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Dose-Dependent Effect of Mammographic Breast Density on the Risk of Contralateral Breast Cancer

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Abstract

Purpose: Increased mammographic breast density is a significant risk factor for breast cancer. It is not clear if it is also a risk factor for the development of contralateral breast cancer.

Methods: The data were obtained from Breast Cancer Surveillance Consortium and included women diagnosed with invasive breast cancer or ductal carcinoma in situ between ages 18 and 88 and years 1995 and 2009. Each case of contralateral breast cancer was matched with three controls based on year of first breast cancer diagnosis, race, and length of follow-up. A total of 847 cases and 2541 controls were included. The risk factors included in the study were mammographic breast density, age of first breast cancer diagnosis, family history of breast cancer, anti-estrogen treatment, hormone replacement therapy, menopausal status, and estrogen receptor status, all from the time of first breast cancer diagnosis. Both univariate and multivariate conditional logistic regression analysis were performed.

Results: In the final multivariate model, breast density, family history of breast cancer, and anti-estrogen treatment remained significant with p-values less than 0.01. Increasing breast density had a dose dependent effect on the risk of contralateral breast cancer. Relative to 'almost entirely fat' category of breast density, the adjusted odds ratios (and p-values) in the multivariate analysis for 'scattered density', 'heterogeneously dense', and 'extremely dense' categories were 1.65 (0.036), 2.10 (0.002), and 2.32 (0.001), respectively.

Conclusion: Breast density is an independent and significant risk factor for development of contralateral breast cancer. This risk factor should contribute to clinical decision making.

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Keywords

contralateral breast cancer; breast density; Breast Cancer Surveillance Consortium; contralateral prophylactic mastectomy

Introduction

In recent years, there has been an alarming rise in the rates of contralateral prophylactic mastectomy (CPM) in patients diagnosed with ductal carcinoma in situ (DCIS) or invasive breast cancer (BC), a majority of which are considered to be medically unnecessary [1–6]. Yet paradoxically the risk for contralateral breast cancer (CBC) has, in fact, decreased over the last few decades [7]. Some recent population-based studies estimate the risk to be 0.1% to 0.3% per year for majority of women [8–14], however, most patients perceive their CBC risk to be as high as 3% per year at the time of their first BC diagnosis [15,16]. Even though some patients diagnosed with unilateral BC indeed have a high risk of developing CBC, for example, those carrying BRCA mutations or having family history of BC, majority of women have much lower risk of developing CBC due to increasing use of effective adjuvant therapies, which has a protective effect on the healthy contralateral breast [17–19]. Thus, there is clearly a need to identify factors that affect the risk of CBC, which can aid in personalized decision making for each patient.

Several risk and protective factors have been identified for CBC. In particular, carrying BRCA 1/2 mutations, younger age at first BC diagnosis, and having family history of BC are associated with higher risks of CBC while getting hormonal therapy for first breast cancer is associated with a lower risk of CBC [20, 21,22]. However, a relatively under-studied factor is mammographic breast density. Utilizing breast density as a risk marker has caught the interest of scientific community only recently. It has been shown that it is a strong risk factor for first breast cancer, with increased density associated with higher risk [23,24]. Thus, it is of interest to study if breast density affects the risk of CBC as well. Some studies have explored this issue for DCIS patients using time to event data and reported increased hazard for developing contralateral invasive BC for patients with higher density [25,26]. More recently, a case- control study reported increased odds ratio for CBC for patients diagnosed with invasive BC [27]. One longitudinal study tracking the changes in breast density over time found that decrease in density is associated with a significantly reduced risk of CBC [28]. Thus, it is imperative to study this highly relevant and timely issue in an in-depth manner using a large population-based cohort.

To this end, we consider the data from the Breast Cancer Surveillance Consortium (BCSC) and study the association between breast density and CBC in patients diagnosed with invasive BC or DCIS after adjusting for factors that are known to affect CBC and/or breast density. We hypothesize that increasing density is associated with higher CBC risk. The availability of a large population-based database of BC patients provides a unique opportunity to investigate such dose-dependent effects, allowing conclusions that are broadly applicable to the US population.

Methods

Data Description

BCSC data have been collected prospectively on women undergoing mammography at seven registries across the US [29]. We used these data to define our case-control dataset. In particular, we considered women whose first BC diagnosis was unilateral and of type invasive and/or DCIS diagnosed between ages of 18 and 88 and years 1995 and 2009. Women who had underwent CPM were excluded. There were a total of 36,169 eligible women whose breast density measurements (at time of the first BC diagnosis) were available as measured using Breast Imaging Reporting and Data System (BI-RADS). Of these, 848 were diagnosed with CBC at least 6 months after their first BC diagnosis, and thus were eligible to be cases for our study. The rest 35,321 were eligible to be used as controls. We selected controls by matching each case to three randomly selected controls. Matching on known risk factors can lead to gains in statistical efficiency of relative risk estimates in case-control studies [30]. The matching was based on race, year of first BC diagnosis, and length of follow-up. For matching on the length of follow-up, a control must have been followed up at least as long as the corresponding case's time to CBC diagnosis. Age at first diagnosis was not used as a matching criterion to allow the possibility of including it in the relative risk model. There were not enough matching controls available for one case, and so this case was discarded. Thus, after matching, our final case-control sample consisted of 847 cases and 2,541 controls. Additional details about the BCSC cohort, variables, and selection criterion can be found elsewhere [29,31].

Statistical Analysis

We first fitted univariate conditional logistic regression models to summarize the unadjusted association of CBC with breast density and six other variables that are known to be associated with CBC and/or breast density. These are age at first BC diagnosis, family history of breast cancer, estrogen receptor (ER) status, anti-estrogen therapy, hormone replacement therapy, and menopausal status. All variables are from the time of first BC diagnosis. Next, to build a multivariate conditional logistic regression model, we followed standard model building steps [32]. In particular, variables whose p-values in univariate analyses were less than 0.25 were initially included [32]. From this preliminary (full) multivariate model, variables were removed if their p-values from likelihood ratio test (LRT) comparing the full and reduced models exceeded 0.05 [32]. This process resulted in the final multivariate model, and the variables that were initially excluded were checked for possible inclusion in the final model by adding them to the model and carrying out LRT. All analyses were conducted using statistical software R [33]. Specifically, the package “survival” [34] was used to fit the conditional logistic regression models. Note that fitting a conditional logistic regression model for matched data is equivalent to maximizing a partial likelihood in the Cox proportional hazards model with respect to regression coefficients [34,35].

Results

In Table 1, we present characteristics of the cases and controls with respect to breast density and other variables, and the univariate results. There are higher proportions of women with

heterogeneously dense and extremely dense breasts among cases (59%) compared to controls (51%) while there is a smaller proportion of women with scattered and almost entirely fat category of breast density among cases (41%) compared to controls (49%). In terms of odds ratio (OR), there appears to be a dose- dependent effect of breast density with denser breasts being associated with higher odds of CBC. Among other factors, age at first diagnosis of less than 40 and having first degree family history of BC are associated with higher odds of CBC while receiving anti-estrogen therapy is associated with reduced odds of CBC, as expected. Hormone replacement therapy and ER status are not significant. Although menopausal status is found to be significant, we note that the significance is driven entirely by the “unknown” category as reflected in the comparison of proportions between cases and controls as well as p-values. As “unknown” is a catch-all category and is not easily interpretable, we do not consider menopausal status in the multivariate analysis.

Table 2 shows results of the multivariate analysis with breast density, family history of BC, and anti- estrogen therapy remaining significant in the final model. Age at first diagnosis was not statistically significant and thus got dropped from the final model. However, due to its clinical significance, we also show results when it is included in the model. The results are the same for other three variables irrespective of whether age at first diagnosis is included or not. We had also explored several other categorizations of age such as (<40, 40–50, 50+), (<40, 40–50, 50–60, 60+), (<30, 30–40, 40+), and (<30, 30–40, 40–50, 50+) as well as including it as a continuous variable, however, in none of those models, age was significant in the multivariate model. The dose-dependent effect of breast density continues to be evident in the final model that has other significant variables as well, with the odds of CBC increasing by 1.65, 2.1, and 2.3 for women with scattered, heterogeneously dense, and extremely dense breasts, respectively, compared to women with almost entirely fat breast density. The ORs for women receiving anti-estrogen therapy (0.72) and having family history of BC (1.4) remained almost the same as in the univariate analysis. We also investigated all two-way interactions between the variables in the final model (including age of first BC diagnosis) but none of them were significant.

Discussion

It is important to identify the factors affecting CBC risk so that a woman diagnosed with unilateral BC can be counseled effectively in a personalized manner regarding her options for treatment, prophylactic measures, and/or surveillance. The issue is underscored by a disturbing trend of increasing rates of CPM amongst women who are, ironically, at lower risks for CBC [36]. Thus, there is a pressing need to uncover and understand the factors related to CBC and translate that knowledge to counseling patients in clinical settings. Breast density is a well-established risk factor for first breast cancer, however, its relationship with CBC is relatively less well-studied. Our study shows that it is an independent and important risk factor for CBC. Moreover we found that increasing breast density is associated with higher CBC risk in a monotonic fashion, that is, there is a dose-dependent effect of breast density.

Similar results have been reported earlier using prospective cohort data and time to second breast cancer modeled with Cox regression [25]. Their reported hazard ratios for CBC are

much higher than ours, in particular, 3.8, 3.9, and 5.0 for the three breast density categories in increasing density (relative to almost entirely fat). This could be because they only studied DCIS patients while we included DCIS as well as invasive BC patients. DCIS patients tend to have a higher risk of CBC, in general [37]. On the other hand, using matched case-control data on invasive BC patients only, a recent paper reported an OR of 1.8 for women with dense breasts compared to those with non-dense breasts [27]. Our reported ORs of 2.32, 2.10, and 1.65 are in-between these two types of results, and is the first one, to the best of our knowledge, to show dose-dependent effect of breast density in invasive and DCIS patients together. We also ran separate analyses for invasive and DCIS patients, and found similar dose-dependent effects in both analyses, albeit the effects are much stronger (with larger ORs) in DCIS patients.

A limitation of our study is that there is a fairly large amount of missing data on several variables (Table 1). This could have reduced the power to detect associations. Moreover, some important variables such as body mass index could not be considered as they had an even larger proportion of missing data rendering them unviable for this analysis. To investigate the sensitivity of the final model to the missing data, we re-fitted the model after excluding women with unknown values of anti-estrogen therapy or family history using unconditional logistic regression. We found virtually no change in results and thus it was reassuring to see that breast density remained an independent risk factor in a complete case analysis. This lends more confidence to our general conclusion about the association between breast density and CBC.

As more and more risk factors get identified for CBC, they can be combined together to do risk prediction for CBC. Some algorithms/models have been already proposed [31, 38], however, they have not been validated yet. Given the importance and timeliness of this problem, more work in identifying risk factors for CBC and translating the knowledge into risk prediction is certainly warranted. The development of improved and personalized CBC risk estimation tools may help reassure women at low risk that they can safely avoid CPM, and thereby help stem the rate of medically unnecessary CPMs.

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Table 1:

Univariate analysis. CI: Confidence Interval

Risk factors	Categories	No. of BC patients (%)		OR (95% CI)	p-value	Overall p-value [*]
		Cases	Controls			
BI-RADS density	Extremely dense	94 (11.10)	230 (9.05)	2.27 (1.37,3.77)	0.002	
	Heterogeneously dense	404 (47.70)	1074 (42.27)	2.08 (1.32,3.3)	0.002	< .001
	Scattered	326 (38.49)	1109 (43.64)	1.64 (1.03,2.6)	0.038	
	Almost entirely fat	23 (2.72)	128 (5.04)	reference		
Age at first BC diagnosis	<40	49 (5.79)	103 (4.05)	1.46 (1.03, 2.07)	0.040	0.116
	40+	798 (94.21)	2438 (95.95)	reference		
Anti-estrogen therapy	Yes	210 (24.79)	786 (30.93)	0.73 (0.61, 0.87)	< 0.001	0.002
	Unknown	88 (10.39)	253 (9.96)	0.96 (0.74, 1.24)	0.740	
	No	549 (64.82)	1502 (59.11)	reference		
First degree family history	Yes	162 (19.13)	372 (14.64)	1.39 (1.13, 1.72)	0.002	0.008
	Unknown	173 (20.43)	543 (21.37)	1.00 (0.80, 1.24)	0.990	
	No	512 (60.45)	1626 (63.99)	reference		
Hormone replacement therapy	Yes	149 (17.59)	473 (18.61)	0.91 (0.73, 1.13)	0.380	0.550
	Unknown	180 (21.25)	566 (22.27)	0.92 (0.75, 1.12)	0.390	
	No	518 (61.16)	1502 (59.11)	reference		
ER status	Negative	145 (17.12)	379 (14.92)	1.20 (0.97, 1.5)	0.100	
	Unknown	256 (30.22)	758 (29.83)	1.06 (0.89, 1.27)	0.510	0.250
	Positive	446 (52.66)	1404 (55.25)	reference		
Menopausal status	Premenopausal	175 (20.66)	532 (20.94)	1.04 (0.85, 1.26)	0.710	0.020
	Perimenopausal	11 (1.30)	42 (1.65)	0.84 (0.43, 1.65)	0.610	
	Unknown	116 (13.70)	250 (9.84)	1.47 (1.15, 1.87)	0.002	
	Postmenopausal	545 (64.34)	1717 (67.57)	reference		

^{*} Overall p-value calculated using likelihood ratio test.

Table 2:

Multivariate analysis. Age at first BC diagnosis is not present in the final model. The last two columns show results with age of first BC diagnosis included. CI: Confidence Interval

Risk factors	Categories	OR (95% CI)	p-value	Overall p-value *	OR	p-value
BI-RADS density	Extremely dense	2.32 (1.39,3.86)	0.001	< 0.001	2.32	0.001
	Heterogeneously dense	2.10 (1.32,3.34)	0.002		2.10	0.002
	Scattered	1.65 (1.03,2.63)	0.036		1.64	0.037
	Almost entirely fat	Reference			Reference	
Anti-estrogen therapy	Yes	0.72 (0.6,0.86)	< 0.001	0.002	0.72	< 0.001
	Unknown	0.95 (0.73,1.24)	0.704		0.95	0.700
	No	Reference			Reference	
First degree history	Yes	1.40 (1.13,1.74)	0.002	0.007	1.40	0.002
	Unknown	0.99 (0.79,1.24)	0.950		0.99	0.953
	No	Reference			Reference	
Age at first BC diagnosis	<40				1.05	0.796
	40+				Reference	

* Overall p-value calculated using likelihood ratio test. Overall p-value of the final model < 0.001