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Estrogen receptor, progesterone receptor, and HER2-neu expression in first primary breast cancers and risk of second primary contralateral breast cancer

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Abstract

Purpose—Breast cancer survivors have a 60% higher risk of developing a second primary asynchronous contralateral breast cancer (CBC) compared to women's risk of developing a first primary breast cancer (FBC). However, little is known about how expression of tumor markers in first breast cancers influence CBC risk.

Methods—We conducted a population-based nested case-control study among women 20–74 years of age diagnosed with a first breast cancer between 1996–2008 in western Washington state to evaluate the association between their tumor's estrogen receptor (ER), progesterone receptor (PR) and HER2-neu (HER2) expression and risk of CBC. The study included 482 cases diagnosed with both a FBC and a CBC and 1,506 control women diagnosed only once with breast cancer identified through our local Surveillance, Epidemiology and End Results (SEER) cancer registry.

Results—Compared to women whose FBC was ER+/PR+, those with ER–/PR– first tumors had a 1.6-fold (95% confidence interval (CI): 1.2–2.3) increased risk of developing a CBC. When evaluated by joint ER/PR/HER2 status, compared to women with ER+/HER2– first cancers those with HER2-overexpressing (ER–/HER2+) and triple-negative disease (ER–/PR–/HER2–) had 2.0-fold (95% CI: 1.1–3.8) and 1.4-fold (95% CI: 0.9–2.3) elevated risks of developing CBC, respectively.

Conclusions—Beyond the known higher risks of mortality among patients diagnosed with more aggressive BC subtypes, here we observe that they may also have increased risks of developing CBC.

Keywords

Breast cancer; Contralateral Breast cancer; Epidemiology

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Introduction

Breast cancer survivors have a 60% higher risk of developing a second primary contralateral breast cancer (CBC) compared to the risk women in the general population have of developing a first primary breast cancer [1]. Although previous studies have evaluated associations between epidemiological factors and CBC risk [2–4,1,5,6], relatively little is known about how expression of tumor markers in first breast cancers may also relate to risk. Further identification and characterization of contributors to CBC risk is of clinical and personal importance to the continuously growing number of breast cancer survivors. We conducted a population-based nested case-control study to evaluate how expression of estrogen receptor (ER), progesterone receptor (PR), and HER2-neu (HER2) in first primary breast cancers is related to CBC risk.

Methods

This case-control study was nested within the cohort of 29,126 women 20–74 years of age diagnosed with a first invasive breast cancer from 1996–2008 in the catchment area of the Cancer Surveillance System (CSS), the population-based cancer registry serving western Washington state. CSS is a participant in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, and it is estimated that >99% of all incident cancer cases in the 13 county area covered by CSS are identified and included in the cancer registry [7]. This study was conducted with institutional review board approval. Potentially eligible cases were the 507 women in the cohort who were subsequently diagnosed with a second primary contralateral invasive breast cancer (CBC) at least six months following the diagnosis of their FBC with follow-up through July 2008.

The study was limited to the 95% of cases (n=482) for which both ER and PR status of their first primary breast cancer (FBC) were known. The diagnosis of a second primary CBC was determined according to SEER rules for defining second primary cancers. SEER does not record breast cancers that are considered recurrences. During the span of this study, a second breast tumor was designated as a recurrence vs. a new primary breast cancer by SEER based on the judgment and clinical determination of the treating physicians, irrespective of the elapsed time between diagnoses of the first and second cancers, the laterality of the two tumors, or any tumor characteristics (e.g., histology or hormone receptor status). We additionally required second primary breast cancers to be diagnosed in the breast contralateral to the first cancer and to have occurred at least six months after the first cancer in order to increase the likelihood that these second cancers represented true second primaries rather than recurrences or synchronous bilateral primaries.

Potential control women diagnosed with a first primary breast cancer but not with a second primary breast cancer were frequency matched to cases by age (within 12 months) at the time of their primary breast cancer diagnosis and year (within 12 months) of FBC diagnosis. Controls must have been alive and CBC-free at the time of their matched case's CBC diagnosis date. Reference dates were assigned to cases and controls; a case's reference date was the date of her CBC diagnosis; a control's reference date corresponded to the date of her

matched case's CBC diagnosis. Of the 1590 potential controls identified, 84 (5%) were excluded from this analysis because they were missing data on either ER or PR status.

Data on covariates that are routinely collected by SEER registries were ascertained through CSS and included various demographic factors (diagnosis date of first breast cancer, race, ethnicity, age at diagnosis), tumor characteristics of both first and second tumors (histology, stage, hormone receptor status), and treatments received for first breast cancer (surgery, radiation, chemotherapy, and hormonal therapy). According to SEER rules, ER and PR status are determined by the pathologist's interpretation of assay values from the most representative tumor specimen. During the years this study was conducted, HER2 status was not routinely collected by CSS. For this analysis, we ascertained HER2 status through the review of pathology reports collected and archived by CSS. A tumor was defined as HER2 negative if it had an immunohistochemistry (IHC) score of 1+ or 0. Tumors with scores of 3+ or 4+ were considered to be HER2 positive. HER2 scores of 2+ are typically considered indeterminate and often a subsequent fluorescent in situ hybridization (FISH) test is done to determine status (102 or 8% of primary breast cancers had 2+ values). Among the first tumors of cases and controls classified as 2+, FISH data were available on 41 and the remainder were classified as HER2 negative given that it has been previously reported that the majority of 2+ HER2 cases are HER2 negative when FISH testing is performed [8]. This was also true in our study where 80% of 2+ HER2 cases that had FISH testing performed were HER2 negative according to their FISH results.

Using logistic regression, we evaluated both joint ER/PR expression and proxies of the three main molecular breast cancer phenotypes defined by ER, PR, and HER2, in relation to risk of developing CBC. For molecular phenotype we grouped tumors into four categories: luminal A (ER+/HER2-) vs. luminal B (ER+/HER2+) HER2-overexpressing (ER-/HER2+), and triple-negative(ER-/PR-/HER2-). The 180 cases (37%) and 528 controls (35%) missing data on HER2 were excluded from these analyses. All analyses were conducted using STATA 10.0 for Windows (Stata Corporation, College Station, Texas). Analyses were adjusted for the variables used for matching (year and age at first breast cancer diagnosis), as well as for histology and stage of the first tumor since these were a priori considered to be potential confounders. In order to assess CBC risk above and beyond the variation that would be expected as a result of differing treatment modalities among women with cancers with different molecular profiles, we also adjusted all analyses for receipt of chemotherapy and receipt of hormonal therapy for the first tumor (any vs. none). We did not additionally adjust for surgery or radiation treatment because their inclusion in the regression models did not alter the risk estimates for any of the queried associations by >10%. We assessed potential effect modification of our results by age at FBC diagnosis (<50 vs. ≥50 years of age), but based on likelihood ratio testing none was observed (p-values for interaction were all >0.05). Given the established benefit of hormonal therapy in reducing CBC risk, we also present an analysis restricted to women who did not receive hormonal treatment for their FBC in order to assess the risk of CBC by tumor subtype independent of hormonal therapy.

In addition, we conducted polytomous regression analyses to assess risks associated with various subtypes of CBC defined by: stage (localized vs. regional/distant); ER/PR status;

and molecular phenotype [ER+/HER2- (luminal A) vs. ER+/HER2+ (luminal B) vs. ER-/HER2+ (HER2 overexpressing) vs. ER-/PR-/HER2- (triple-negative)].

Results

Cases and controls were similar with respect to their age and race (Table 1). The FBC of cases were somewhat less likely than those of controls to be ductal (77.6% and 80.1%, respectively) and of regional/distant stage (29.2% vs. 34.4%, respectively). With respect to FBC treatments, a similar proportion of cases and controls received a total mastectomy or radiation therapy and cases were somewhat less likely than controls to have received either chemotherapy or adjuvant hormonal therapy for their primary breast cancer (46.9% vs. 53.4%; and 58.3% vs. 62.1%, respectively).

Women who had an ER-/PR- FBC had a 60% higher risk of developing a CBC (OR: 1.6, 95% CI: 1.2–2.3; Table 2) compared to women with an ER+/PR+ FBC. This association was stronger among women in whom more time had elapsed between their first breast cancer diagnosis and their reference date; compared to women with an ER+/PR+ FBC, those with an ER-/PR- FBC had a 2.9-fold higher risk of developing a CBC greater than 5 years after their FBC diagnosis.

Women with HER2-overexpressing and triple-negative FBC had elevated risks of developing a CBC (OR: 2.0, 95% CI: 1.1–3.8 and OR: 1.4, 95% CI: 0.9–2.3, respectively; Table 3) relative to women with a luminal-A FBC though the risk among triple-negative patients was within the limits of chance. The association between triple-negative FBC and CBC appeared to be limited to those women in whom four or more years had elapsed between their first and contralateral breast cancer. To the extent that we were able to evaluate the relationship (given our limited follow-up) there did not appear to be a clear threshold of time beyond which risk reached a plateau.

Risk of localized CBC was similar across first tumors divided by ER/PR status or joint ER/PR/HER2 status (Tables 2 and 3). In contrast, relative to women whose first tumors were ER+/PR+, those with ER-/PR- tumors had a 2.3-fold (95% CI: 1.3–3.9) higher risk of being diagnosed with regional/distant stage CBC. Similarly, compared to women whose first tumors were luminal, those with HER2-overexpressing and triple-negative tumors had increased risks (OR: 3.4, 95% CI: 1.2–9.3 and OR: 3.1, 95% CI: 1.4–7.1, respectively) of being diagnosed with an advanced stage CBC.

The risk of developing and ER+/PR+ CBC was similar across women diagnosed with a first primary ER+/PR+, ER+/PR-, or a ER-/PR- breast cancer. In contrast, compared to women diagnosed with a first primary ER+/PR+ breast cancer, those diagnosed with a ER-/PR- breast cancer had a 6.7 fold (95%CI: 3.8–11.8) higher risk of developing a ER-/PR- CBC (table 2). Similarly, compared to women diagnosed with a first primary luminal-A breast cancer, those diagnosed with a triple-negative breast cancer had a 7.5-fold higher risk of developing a triple-negative CBC (95%CI: 2.7–20.5; Table 3). There were too few HER2-overexpressing CBC to allow a separately evaluation of concordance between first and contralateral HER2-overexpressing breast tumors.

Of note, the patterns of results shown in Table 2 and Table 3 did not change appreciably when the analysis was restricted to women who did not receive adjuvant hormonal therapy for their FBC.

Discussion

We observed that women with ER–/PR– FBC had a higher risk of contralateral breast cancer, than women with ER+/PR+ FBC. Similarly, we found that women whose first cancer was either HER2-overexpressing or triple-negative had a higher risk of contralateral breast cancer relative to women with a luminal-A first breast cancer. Our results with respect to HER2-overexpressing breast cancer do need to be interpreted with some caution though given that this was the smallest of our case groups. Risk estimates were within the limits of chance when the analysis was restricted to breast cancer patients who did not receive adjuvant hormonal therapy, though the direction and magnitude of our risk estimates were the similar to our overall analysis. For women with HER2-overexpressing breast cancer this elevation in risk was observed regardless of the timing of the second CBC, while for ER–/PR– patients (including those who had triple-negative first breast cancers) the increase in risk was confined to CBCs diagnosed at least 3 years after their first breast cancer. While the reason for this difference is unclear and it could be a chance finding, it could also be a reflection of the protective effect of chemotherapy among ER–/PR– and triple-negative patients more proximal to the time therapy was administered. The presence of a similar pattern of results among the subgroup of women who had received no hormone treatment for their FBC suggests that these findings are not a reflection of a chemo-preventive effect of hormone therapy among women with ER+ FBC. Additionally, patients with HER2-overexpressing or triple-negative tumors also had elevated risks of developing an advanced stage CBC. These findings suggest that in addition to the elevated risks of recurrence and death that patients with triple-negative or HER2-overexpressing breast cancers experience [9–11], they also have an elevated risk of CBC, and particularly of advanced stage CBC.

Although several studies have evaluated the association between tumor characteristics, such as histology and stage, as well as demographic characteristics and CBC risk, only two have evaluated the association between hormone receptor and HER2 status and CBC risk [10,6]. We previously found no difference in risk of CBC between young women with hormone receptor negative or positive FBC, but did find that women whose first tumor was HER2 positive had a higher risk of CBC than did women with HER2 negative FBC. However this analysis was restricted to women under the age of 45 and is not directly comparable to the predominantly older population included in this study. Findings from the study by Bessenova, *et al.*, however, were similar to our results. They found that women with triple-negative and HER2-overexpressing FBC had standardized incidence ratio (SIR) of 1.84 and 1.92, respectively, of developing a second breast cancer, while women who were ER+ and/or PR+ and HER2+ had a SIR of 0.93 [10]. Although they did not have HER2 information, the findings of Kurian, *et al* [12], are also similar to those reported here. They observed that women with ER–/PR– first breast cancers had almost double the risk of developing a contralateral tumor than women with a FBC that was either ER+ or PR+ (SIR: 3.57 and 2.22, respectively). Bouchardy, *et al.* [13]. found that women with ER– FBC had an almost three-fold higher risk of developing a CBC than women with an ER+ FBC.

Strengths of the current study include its population-based design and its duration of follow-up that allowed us to evaluate the temporal effects that seem to modify the association between breast cancer subtype and subsequent risk of CBC.

Similar to our results, both Kurian, *et al.* [12] and Bouchardy, *et al.* [13] found a high correlation between the hormone receptor status of the first and second tumor; among women with a hormone receptor negative first cancer the risk of developing another hormone receptor negative breast cancer was substantially higher than the risk of developing a hormone receptor positive second cancer (SIR 9.81 and 1.94 of developing a hormone receptor negative vs. a hormone receptor positive second primary, respectively in the study by Kurian, *et al.*, and SIR 7.94 and 1.02 of developing an ER– vs. ER+ second primary in the study by Bouchardy, *et al.*). This high correlation is likely a reflection that both genetic and non-genetic factors contributing to the development of a first breast cancer of a particular type would also contribute to the development of a breast cancer of the same type in the contralateral breast [14]. An example of this is women who are BRCA1 mutation carriers. These women have an increased risk of developing triple-negative breast cancers, as it has been estimated that 20% of women with triple-negative breast cancer are BRCA1 mutation carriers [15], and also have a four-fold higher risk of developing a CBC following a FBC compared to non-BRCA1 mutation carriers [16].

It is important to acknowledge the potential limitations of this study. By relying only on data from the SEER registry we were unable to adjust for factors known to influence breast cancer risk, such as family history, parity, and hormone use that are not collected by SEER. Since pathological features of each woman's breast tumor are evaluated at the institution where the diagnosis is made, it is possible that there may be differences in categorization of histology, stage, hormone receptor status and molecular sub-typing, however, these differences are unlikely to be systematic, and therefore will likely only have minimized our ability to detect associations between exposures and outcomes of interest by biasing our associations toward the null. Lastly, given our reliance on cancer registry data there is potential for misclassification of recurrences as second primaries and vice-versa. While the extent and resulting biases from this misclassification are unknown, we attempted to limit this by restricting our second primary cases to those that were both contralateral and diagnosed at least 6 months after the first primary breast cancer. Despite being based on a large underlying cohort, an additional limitation of this study relates to the few number of CBC events observed particularly among the less common subtypes of breast cancer. Consequently, larger studies are needed to confirm our observations.

As a result of early detection and improving treatments for breast cancer there is a continuously growing population of breast cancer survivors, and so it is becoming increasingly important to identify those survivors who carry a particularly high risk for developing CBC. This information can help guide a woman's treatment as well as her follow-up and screening choices. Here we observed that beyond their known higher risk of mortality, patients with more aggressive BC subtypes also have increased risks of developing CBC, and particularly more advanced stage CBC. If confirmed, these patients may warrant more frequent or multi-modal screening of their contralateral breast, though further studies are needed to evaluate the potential benefits of such approaches.

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Table 1

Selected characteristics of contralateral breast cancer cases and control women diagnosed only once with breast cancer

Characteristic	Controls (n=1506) n %	Cases (n=482) n %
Age at first breast cancer diagnosis		
20–39	113 (7.5)	37 (7.7)
40–49	343 (22.8)	92 (19.1)
50–59	455 (30.2)	135 (28.0)
60–73	595 (39.5)	218 (45.2)
Diagnosis year of first tumor		
1996–1997	372 (24.7)	142 (29.5)
1998–1999	437 (29.0)	136 (28.2)
2000–2001	327 (21.7)	96 (19.9)
2002–2003	209 (13.9)	61 (12.7)
2004–2008	161 (10.7)	47 (9.8)
Race		
White	1383 (92.0)	445 (92.9)
Black	68 (4.5)	19 (4.0)
Asian	46 (3.1)	12 (2.5)
Other	7 (0.5)	3 (0.6)
Missing	2	3
Stage of first tumor		
Local	946 (65.4)	333 (70.7)
Regional/Distant	500 (34.6)	138 (29.3)
Missing	60	11
Histology of first tumor		
Ductal	1087 (80.0)	339 (77.8)
Lobular	127 (9.4)	45 (10.3)
Mixed ductal/lobular	130 (9.6)	49 (11.2)
Other	14 (1.0)	3 (0.7)
Missing	148	46
Surgery		
None	30 (2.0)	4 (0.8)
Partial mastectomy	959 (63.7)	304 (63.1)
Total mastectomy	517 (34.3)	174 (36.1)
Radiation		
No	431 (28.8)	143 (29.7)
Yes	1064 (71.2)	339 (70.3)

Characteristic	Controls (n=1506) n %	Cases (n=482) n %
Missing	11	0
Chemotherapy		
No	699 (46.7)	256 (53.1)
Yes	798 (53.3)	226 (46.9)
Missing	9	0
Adjuvant hormonal therapy		
No	562 (37.6)	202 (41.9)
Yes	931 (62.4)	280 (58.1)
Missing	13	0

Table 2

Hormone receptor status first tumor								
Characteristic	ER+/PR+			ER+/PR−			ER−/PR−	
	Controls n (%)	Cases n (%)	OR* (95% CI)	Controls n (%)	Cases n (%)	OR* (95% CI)	Controls n (%)	Cases n (%)
All women, irrespective of receipt of hormone therapy								
All CBC cases	1077 (71.5)	314 (65.1)	1.00 (ref)	161 (10.7)	55 (11.4)	1.2 (0.8–1.7)	268 (17.8)	113 (23.4)
Time between FBC and CBC diagnoses								
> 1 year	1004 (71.3)	286 (63.3)	1.00 (ref)	151 (10.7)	54 (11.9)	1.2 (0.9–1.8)	253 (18.0)	112 (24.8)
> 2 years	818 (72.1)	241 (63.4)	1.00 (ref)	121 (10.7)	48 (12.6)	1.4 (0.9–2.0)	195 (17.2)	91 (23.9)
> 3 years	706 (72.8)	209 (63.9)	1.00 (ref)	102 (10.5)	43 (13.1)	1.4 (0.9–2.1)	162 (16.7)	75 (22.9)
> 4 years	581 (74.2)	175 (64.6)	1.00 (ref)	81 (10.3)	34 (12.5)	1.4 (0.9–2.2)	121 (15.5)	62 (22.9)
> 5 years	463 (74.2)	121 (58.7)	1.00 (ref)	65 (10.4)	31 (15.0)	1.8 (1.1–3.0)*	96 (15.4)	54 (26.2)
CBC Stage								
Local Stage CBC	1077 (71.5)	185 (67.5)	1.00 (ref)	161 (10.7)	34 (12.4)	1.2 (0.8–1.9)	268 (17.8)	55 (20.1)
Regional/Distant Stage CBC	1077 (71.5)	77 (61.6)	1.00 (ref)	161 (10.7)	11 (8.8)	0.9 (0.4–1.7)	268 (17.8)	37 (29.6)
CBC ER/PR status								
ER+PR+	1077 (71.5)	182 (75.5)	1.00 (ref)	161 (10.7)	26 (10.8)	0.9 (0.6–1.5)	268 (17.8)	33 (13.7)
ER+PR−	1077 (71.5)	55 (72.4)	1.00 (ref)	161 (10.7)	10 (13.2)	1.2 (0.6–2.4)	268 (17.8)	11 (14.5)
ER−PR−	1077 (71.5)	43 (37.7)	1.00 (ref)	161 (10.7)	10 (8.8)	1.4 (0.7–3.0)*	268 (17.8)	61 (53.5)
Women whose first breast cancer was not treated with hormone therapy								
All CBC cases	290 (51.6)	100 (49.5)	1.00 (ref)	46 (8.2)	11 (5.4)	0.8 (0.4–1.7)	226 (40.2)	91 (45.0)
Time between FBC and CBC diagnoses								
> 1 year	279 (52.1)	93 (47.7)	1.00 (ref)	43 (8.0)	11 (5.6)	0.9 (0.4–1.9)	214 (39.9)	91 (46.7)
> 2 years	234 (53.4)	79 (48.8)	1.00 (ref)	33 (7.5)	9 (5.6)	0.9 (0.4–2.2)	171 (39.0)	74 (45.7)
> 3 years	206 (55.5)	68 (51.1)	1.00 (ref)	26 (7.0)	7 (5.3)	0.8 (0.3–2.2)	139 (37.5)	58 (43.6)
> 4 years	171 (59.0)	56 (50.9)	1.00 (ref)	16 (5.5)	5 (4.5)	1.1 (0.4–3.2)	103 (35.5)	49 (44.5)

Hormone receptor status first tumor									
Characteristic	ER+/PR+			ER+/PR-			ER-/PR-		
	Controls n (%)	Cases n (%)	OR* (95% CI)	Controls n (%)	Cases n (%)	OR* (95% CI)	Controls n (%)	Cases n (%)	OR* (95% CI)
> 5 years	140 (59.8)	40 (45.5)	1.00 (ref)	13 (5.6)	5 (5.7)	1.4 (0.4-4.3)	81 (34.6)	43 (48.9)	2.6 (1.4-5.0)*
CBC Stage									
Local Stage CBC	290 (51.6)	66 (56.4)	1.00 (ref)	46 (8.2)	7 (6.0)	0.9 (0.4-2.2)	226 (40.2)	44 (37.6)	1.3 (0.8-2.2)
Regional/Distant Stage CBC	291 (51.6)	16 (34.8)	1.00 (ref)	--	--	--	227 (40.2)	29 (63.0)	2.2 (1.0-4.7)
CBC ER/PR status									
ER+/PR+	290 (51.6)	67 (66.3)	1.00 (ref)	46 (8.2)	8 (7.9)	0.8 (0.3-2.0)	226 (40.2)	26 (25.7)	0.7 (0.4-1.4)
ER+/PR-	291 (51.6)	13 (50.0)	1.00 (ref)	--	--	--	227 (40.2)	10 (38.5)	1.0 (0.3-2.8)
ER-/PR-	290 (51.6)	11 (19.0)	1.00 (ref)	--	--	--	226 (40.2)	47 (81.0)	4.0 (1.8-9.1)*

Note: FBC=first breast cancer; CBC=contralateral breast cancer; OR=odds ratio; CI=confidence interval

* ORs adjusted for histology, stage, chemotherapy, hormones, age at first BC dx and reference date

[†] p<0.05.

Table 3

Contralateral breast cancer risk according to the joint ER/PR/HER2 expression of the first breast cancer

Characteristic	ER/PR/HER2 expression of the first breast cancer						ER-/HER2+ (HER2 overexpressing)						ER-/PR-/HER2- (triple-negative)					
	ER+/HER2- (luminal A)			ER+/HER2+ (luminal B)			ER-/HER2+ (HER2 overexpressing)			ER-/PR-/HER2- (triple-negative)			ER-/PR-/HER2- (triple-negative)			ER-/PR-/HER2- (triple-negative)		
	Controls n (%)	Cases n (%)	OR* (95% CI)	Controls n (%)	Cases n (%)	OR* (95% CI)	Controls n (%)	Cases n (%)	OR* (95% CI)	Controls n (%)	Cases n (%)	OR* (95% CI)	Controls n (%)	Cases n (%)	OR* (95% CI)	Controls n (%)	Cases n (%)	OR* (95% CI)
All women, irrespective of receipt of hormone therapy																		
All CBC cases	698 (71.4)	200 (66.2)	1.00 (ref)	121 (12.4)	29 (9.6)	0.8 (0.5–1.4)	46 (4.7)	25 (8.3)	2.0 (1.1–3.8)*	113 (11.6)	48 (15.9)	1.4 (0.9–2.3)						
Time between FBC and CBC diagnoses																		
>1 year	651 (71.2)	187 (65.8)	1.00 (ref)	115 (12.6)	25 (8.8)	0.8 (0.5–1.3)	41 (4.5)	25 (8.8)	2.2 (1.2–4.3)*	107 (11.7)	47 (16.5)	1.4 (0.9–2.4)						
> 2 years	520 (70.4)	151 (66.2)	1.00 (ref)	98 (13.3)	20 (8.8)	0.8 (0.5–1.4)	31 (4.2)	18 (7.9)	2.1 (1.0–4.4)	90 (12.2)	39 (17.1)	1.5 (0.9–2.7)						
> 3 years	441 (72.3)	127 (66.8)	1.00 (ref)	77 (12.6)	19 (10.0)	1.0 (0.6–1.8)	25 (4.1)	14 (7.4)	2.4 (1.0–5.7)*	67 (11.0)	30 (15.8)	1.8 (1.0–3.4)						
> 4 years	357 (73.5)	103 (67.3)	1.00 (ref)	65 (13.4)	15 (9.8)	0.9 (0.5–1.7)	16 (3.3)	11 (7.2)	2.7 (1.0–7.4)*	48 (9.9)	24 (15.7)	2.2 (1.1–4.3)*						
> 5 years	283 (73.7)	78 (66.1)	1.00 (ref)	45 (11.7)	10 (8.5)	1.1 (0.5–2.4)	15 (3.9)	9 (7.6)	3.1 (1.0–9.0)*	41 (10.7)	21 (17.8)	2.7 (1.3–5.7)*						
CBC Stage																		
Local Stage CBC	755 (70.6)	129 (72.1)	1.00 (ref)	136 (12.7)	15 (8.4)	0.6 (0.3–1.2)	51 (4.8)	10 (5.6)	1.7 (0.8–3.7)	128 (12.0)	25 (14.0)	1.2 (0.6–2.2)						
Regional/Distant Stage CBC	755 (70.6)	39 (51.3)	1.00 (ref)	136 (12.7)	11 (14.5)	1.7 (0.8–3.6)	51 (4.8)	9 (11.8)	3.4 (1.2–9.3)*	128 (12.0)	17 (22.4)	3.1 (1.4–7.1)*						
CBC ER/PR/HER2 status																		
ER+/HER2-	755 (70.6)	160 (89.9)	1.00 (ref)	--	--	--	--	--	--	128 (12.0)	18 (10.1)	0.6 (0.3–1.3)						
ER-/PR-/HER2-	755 (70.6)	17 (41.5)	1.00 (ref)	--	--	--	--	--	--	128 (12.0)	24 (58.5)	7.5 (2.7–20.5)*						
Women whose FBC was not treated with hormone therapy																		
All CBC cases	159 (47.3)	58 (45.0)	1.00 (ref)	38 (11.3)	12 (9.3)	1.0 (0.5–2.1)	41 (12.2)	23 (17.8)	2.1 (1.0–4.3)	98 (29.2)	36 (27.9)	1.2 (0.6–2.2)						
Time between FBC and CBC diagnoses																		
>1 year	154 (48.1)	56 (44.8)	1.00 (ref)	35 (10.9)	10 (8.0)	0.9 (0.4–1.9)	36 (11.3)	23 (18.4)	2.3 (1.1–4.9)*	95 (29.7)	36 (28.8)	1.1 (0.6–2.1)						
> 2 years	123 (46.6)	46 (46.0)	1.00 (ref)	31 (11.7)	7 (7.0)	0.7 (0.3–1.7)	28 (10.6)	17 (17.0)	1.8 (0.8–4.4)	82 (31.1)	30 (30.0)	1.2 (0.6–2.3)						
> 3 years	107 (50.0)	38 (48.1)	1.00 (ref)	25 (11.7)	7 (8.9)	0.9 (0.4–2.4)	23 (10.7)	13 (16.5)	2.1 (0.8–5.6)	59 (27.6)	21 (26.6)	1.4 (0.6–3.2)						
> 4 years	84 (51.9)	31 (49.2)	1.00 (ref)	23 (14.2)	4 (6.3)	0.5 (0.2–1.7)	15 (9.3)	10 (15.9)	2.0 (0.6–6.5)	40 (24.7)	18 (28.6)	1.7 (0.7–4.3)						

ER/PR/HER2 expression of the first breast cancer												
Characteristic	ER+/HER2- (luminal A)			ER-/HER2+ (luminal B)			ER-/HER2+ (HER2 overexpressing)			ER-/PR-/HER2- (triple-negative)		
	Controls n (%)	Cases n (%)	OR* (95% CI)	Controls n (%)	Cases n (%)	OR* (95% CI)	Controls n (%)	Cases n (%)	OR* (95% CI)	Controls n (%)	Cases n (%)	OR* (95% CI)
> 5 years	72 (53.7)	24 (46.2)	1.00 (ref)	15 (11.2)	4 (7.7)	1.0 (0.3–3.6)	14 (10.4)	9 (17.3)	2.7 (0.8–9.5)	33 (24.6)	15 (28.8)	2.2 (0.8–6.0)
Stage of CBC												
Local Stage CBC	177 (46.9)	36 (50.0)	1.00 (ref)	43 (11.4)	8 (11.1)	1.0 (0.4–2.5)	45 (11.9)	10 (13.9)	2.2 (0.9–5.5)	112 (29.7)	18 (25.0)	1.0 (0.4–2.1)
Regional/Distant Stage CBC	177 (46.9)	10 (29.4)	1.00 (ref)	44 (11.4)	3 (8.8)	1.4 (0.3–5.6)	46 (11.9)	8 (23.5)	3.3 (0.9–11.5)	113 (29.7)	13 (38.2)	3.0 (1.0–8.8) *
Molecular subtype CBC												
Luminal FBC	177 (46.9)	55 (82.1)	1.00 (ref)	--	--	--	--	--	--	112 (29.7)	12 (17.9)	0.3 (0.1–0.9) *
Triple negative FBC	177 (46.9)	3 (12.5)	1.00 (ref)	--	--	--	--	--	--	112 (29.7)	21 (87.5)	10.1 (2.3–43.3) *

FBC= first breast cancer; CBC= contralateral breast cancer; OR= odds ratio; CI= confidence interval; OE= over expressed

* ORs adjusted for age at first breast cancer diagnosis, reference date, histology, stage, chemotherapy, and hormonal therapy.

[†] p<0.05.