Reproductive History and Risk of Second Primary Breast Cancer: The WECARE Study

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Abstract

Background: **Women with an initial breast cancer diagnosis are at elevated risk of developing subsequent cancer in the contralateral breast. Studies of reproductive factors and contralateral breast cancer (CBC) have provided inconsistent results.**
Methods: **We employed a case-control study nested within five population-based cancer registries in the United States and Denmark to examine associations between reproductive history and CBC risk. Cases were women with asynchronous CBC who had their first primary invasive breast cancer before age 55 years. Two controls, who had only one primary breast cancer diagnosis, were individually matched to each case on age and year of diagnosis, race, and registry. A total of 694 case-control triplets and 11 case-control pairs were enrolled. Information regarding possible CBC risk factors was obtained via telephone interviews. Multivariable conditional logistic regression was used to estimate rate ratios (RR) and 95% confidence intervals (95% CI) associated with risk factors of interest.**
Results: **Increasing number of full-term pregnancies (FTP) was inversely associated with CBC risk (*P* trend, 0.001). Women who reported menarche before age 13 years had an increased risk of CBC (RR, 1.26; 95% CI, 1.01-1.58). Age at first FTP, breastfeeding history, and age at menopause were not significantly associated with CBC risk.**
Conclusions: **These results suggest age at menarche and parity, which are established risk factors for first primary breast cancer, are associated with CBC, whereas other reproductive risk factors associated with first primary breast cancer, such as age at first FTP, are less important factors in the development of CBC.** (Cancer Epidemiol Biomarkers Prev 2007;16(5):906–11)

Introduction

Women diagnosed with breast cancer have greater risk for a second primary breast cancer than the general population of women has for a first primary breast cancer (1). This risk differential seems to be higher for women who are under age 45 at the time of their initial breast cancer diagnosis than it is for older women (1-5). Several factors have been investigated in relation to risk of contralateral breast cancer (CBC), including genetic predisposition and family history (2, 3, 5-8), reproductive history (2-4, 7-9), histology of the first breast cancer (3, 10, 11), treatment (3, 7, 9, 11), anthropometry (3, 4), and race (11).

The impact of pregnancy on risk of a first primary breast cancer has been extensively studied (12). Although having a full-term pregnancy (FTP) is associated with reduced breast cancer risk among postmenopausal women overall, women who have their first term pregnancy in their 30s or 40s are at somewhat higher breast cancer risk than nulliparous women. The immediate effect of a term pregnancy seems to increase a woman's risk, with the duration of this elevated risk decreasing with each subsequent pregnancy (13). Studies of pregnancy history and risk of CBC have provided inconsistent results with some reporting that late age at first FTP (2) and low parity or nulliparity (2, 7, 9, 14) are associated with increased risk of CBC, whereas others report no significant associations between reproductive factors and CBC risk (4, 8, 15).

The number of breast cancer survivors is increasing due to rising rates of both breast cancer incidence (16) and survival (17). Identifying factors that are associated with an increased risk of asynchronous CBC is therefore more important for developing strategies of early detection of this outcome. To resolve some of the inconsistencies of prior studies regarding the relationship of pregnancy history to risk of CBC, we employed a case-control study nested among a large sample of breast cancer patients in five population-based cancer registries to examine further this relationship and to determine whether the observed associations are modified by other risk factors.

Materials and Methods

The WECARE Study is a multicenter, population-based nested case-control study that involves a comparison of women with asynchronous bilateral breast cancer, who serve as case subjects, with women with unilateral breast cancer, who serve as control subjects (18). All participants were identified through a cohort of five population-based tumor registries, four in the United States: Los Angeles County Cancer Surveillance Program; Cancer Surveillance System of the Fred Hutchinson Cancer Research Center (Seattle region); State Health Registry of Iowa; and Cancer Surveillance Program of Orange County/San Diego-Imperial Organization for Cancer Control (Orange County/San Diego), all of which participate in (or are members of) the National Cancer Institute Surveillance, Epidemiology and End Results program. The

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one participating Scandinavian registry was the Danish Breast Cancer Cooperative Group Registry supplemented by data from the Danish Cancer Registry.

Study Population

Eligibility. Women were eligible as cases if they met the following criteria: (*a*) diagnosed between January 1, 1985, and December 31, 1999, with a first primary invasive breast cancer that did not spread beyond the regional lymph nodes at diagnosis and a second primary *in situ* or invasive breast cancer diagnosed in the contralateral breast at least 1 year after the first breast cancer diagnosis and before January 1, 2002; (*b*) resided in the same study reporting area for both diagnoses; (*c*) had no previous or intervening cancer diagnosis except squamous cell or basal cell skin cancer or cervical carcinoma *in situ*; (*d*) were alive at the time of contact, and able to provide informed consent to complete the interview; and (*e*) were under age 55 years at the time of diagnosis of the first primary breast cancer.

Two control subjects were individually matched to each case on year of birth (5-year strata), year of diagnosis (4-year strata), registry region, and race, and were counter-matched on registry-reported radiation exposure (18). Counter-matching was done so that two of the members of each case-control triplet were reported to have radiation exposure by registry records. This counter-matching was carried out to address the hypotheses of the main study, designed to assess whether genetic factors involved in DNA repair, in combination with radiation exposure, were associated with an increased risk of second primary breast cancer. In selecting controls, we created an at-risk interval which was the elapsed time (in days) between the matched case's two diagnoses. This interval was added to the date of breast cancer diagnosis for the control to define her reference date for the purposes of eligibility (she had to have lived in the same cancer-reporting region on that date) and interview. In addition, controls had to meet the following criteria: (*a*) diagnosed since January 1, 1985, with first primary invasive breast cancer that did not spread beyond the regional lymph nodes at diagnosis, while residing in one of the study reporting areas; (*b*) no diagnosis of any other cancer before her breast cancer diagnosis or in the defined at-risk interval (other than squamous or basal cell skin carcinoma or *in situ* cervical cancer); (*c*) alive at the time of contact and able to provide informed consent to complete the interview; and (*d*) no prophylactic mastectomy of the contralateral breast before or within the at-risk interval.

Across the five tumor registries, a total of 998 women with bilateral breast cancer were eligible and approached for inclusion in the study as cases, and 2,112 women with unilateral breast cancer were eligible as controls. Of these potential participants, 708 (71%) cases and 1,399 (66%) controls completed the interview and had a blood sample drawn. In all, we successfully recruited 694 counter-matched triplets (1 case: 2 controls), where two members of each triplet were exposed to radiation according to the registry records. For 17 triplets, the region or the race/ethnicity criteria was relaxed. We also recruited 11 case-control pairs, of which 8 sets were discordant on radiation exposure and 3 were concordant on exposure. We were unable to recruit any controls for three cases. Of the 998 cases and 2,112 controls eligible and approached for the study, reasons for nonparticipation, in sequence, were physician refusal (0.5% cases, 1% controls), subject interview refusal (27% cases, 31% controls), and subject blood draw refusal (3% cases, 3% controls).

Data Collection. All participants in the WECARE Study were interviewed by telephone using a structured questionnaire. The interview was conducted by a trained interviewer. The questionnaire emphasized events occurring before the diagnosis of the first primary as well as those that occurred within the at-risk period (before the reference date for the case or the control subject). The focus of the questionnaire was on known or suspected risk factors for breast cancer, including personal demographics, medical history, family history, reproductive history, use of hormones, body size, and alcohol intake. The section on reproductive history included age at menarche, number of pregnancies, pregnancy outcome, duration and end date for each pregnancy, lactation history, menopausal status, and age at menopause. Medical records, pathology reports, and hospital charts were used to collect detailed treatment information (chemotherapy, hormonal therapy, and radiation therapy). Because the medical record data contained missing values regarding chemotherapy (7%) and/or hormonal therapy (10%), the treatment history variable was defined using self-reported data for these subjects. Information on tumor characteristics (including location in the breast, stage at diagnosis, estrogen and progesterone receptor status, and histology) was collected from medical records or cancer registry records. The study protocol was approved by the Institutional Review Boards at each study site and by the ethical committee system in Denmark.

Statistical Methods. Two members of each triplet were radiation exposed, and one was radiation unexposed, based on treatment history information recorded in each of the cancer registries (counter-matching design). Standard techniques for analyzing counter-matched case-control studies (19) were employed to investigate the individual and joint effects of known risk factors on the development of CBC. Log-linear (Cox) models for CBC rates were fit to the individually matched triplet data using conditional logistic regression with the inclusion of a log weight covariate in the model where the coefficient of this log weight was fixed at 1 (i.e., an offset in the model). These computed weights were incorporated in the models to account for the sampling probability of counter-matching. They are based on the number of radiation-exposed and unexposed subjects within the sampled risk set. Aside from this offset term, the analytic approach is identical to a standard conditional logistic regression analysis for individually matched case-control studies.

In the current study, we focused on the following reproductive variables: age at menarche (<13, ≥13 years); pregnancy history (never pregnant, no FTP, and at least one FTP); number of FTP (nulliparous, 1, 2, 3, 4+); age at first FTP (<20, 20-24, 25-29, 30+ years or nulliparous); age at menopause (premenopausal, postmenopausal age <45 years, postmenopausal age ≥45 years), breast-fed (never/ever), and duration of breastfeeding (1-3, 4-6, 7-23, 24+ months). A FTP was defined as any stillbirth, livebirth, or multiple births with at least one live birth. Menopausal status was determined by comparing date or age at last period with reference date: if the subject reported that she was still having periods, was having periods within 12 months of the reference date, or was currently pregnant, she was considered to be premenopausal; if subject reported that her periods stopped at least 1 year before her reference date, she was considered to be postmenopausal as of the reference date. Pregnancy and lactation history were first considered through the date of first breast cancer diagnosis and then through the end date for the at-risk period (denoted ''as of reference date,'' the date of CBC diagnosis for the cases and the corresponding date for the matched controls). Rate ratios and corresponding 95% confidence intervals (95% CI) were estimated by fitting univariate and multivariable conditional logistic regression models accounting for the counter-matched sampling. In the multivariable analyses, we included all of the following risk factors: exact age at diagnosis of the first primary breast cancer, family history of breast cancer (no first-degree affected relatives, at least one first-degree affected relative, adopted or unknown family history), histology of first primary (lobular, medullary, ductal, or other) stage of the first

primary (localized, regional), first primary treatment history of chemotherapy and/or any hormone therapy (yes, no), and radiation therapy (yes, no). Adjusted linear trend test *P* values were obtained by including in the multivariable models variables that assigned values 1, 2, 3, 4, etc. to the different nominal categories. All statistical tests were two sided.

Total numbers presented in the tables may vary slightly due to missing information. To account for missing information within a counter-matched set, a missing indicator variable was included in the conditional logistic regression models according to the methods proposed by Huberman and Langholz (20).

Results

Distributions of the matching factors and other characteristics for the cases and controls are displayed in Table 1. The large difference in frequencies of radiation exposure between cases and controls was due to the counter-matching in the design whereby each triplet was comprised of two exposed subjects and one unexposed.

Women who experienced menarche before age 13 had a modest and marginally significant increased risk of CBC [rate ratio (RR), 1.26; 95% CI, 1.01-1.58; Table 2]. Gravidity and menopausal status were not statistically significantly associated with CBC. The number of FTPs (as of reference date) was inversely associated with risk (*P* trend = 0.001) and culminated in a 50% reduction in risk of CBC for cases with four or more FTPs. We observed an increased rate ratio for women who were nulliparous or had their first FTP at age 30 or later in the unadjusted analysis. If we consider these groups separately, the rate ratio for the nulliparous group as compared with age <20 is 1.46 (95% CI, 0.98-2.18), whereas the rate ratio for the 30+ group relative to age <20 is 1.62 (95% CI, 1.06-2.47). However, after considering the number of term pregnancies and other potential confounders in the multivariable model, age at first FTP was not significantly associated with the risk of CBC (*P* trend = 0.76). Analyses of the number of births occurring before or after age 30 were also completed. As

Table 1. Characteristics of 2,107 women with unilateral and bilateral breast cancer included in the WECARE study

	Bilateral (*N* = 708)	Unilateral (*N* = 1,399)
Matched characteristics		
Registry, *n* (%)		
Iowa	113 (16)	222 (16)
Orange County/San Diego	118 (17)	231 (17)
Los Angeles County	199 (28)	390 (28)
Seattle	99 (14)	198 (14)
Denmark	179 (25)	358 (26)
Race, *n* (%)		
Non-Hispanic white	649 (91.7)	1,288 (92.1)
Hispanic white	24 (3.3)	48 (3.4)
Black	21 (3)	39 (2.8)
Chinese	2 (0.3)	3 (0.2)
Japanese	2 (0.3)	4 (0.3)
Filipino	7 (1)	14 (1)
Other Asian	2 (0.3)	1 (0.1)
Subject's age at first breast cancer diagnosis, mean (range)	46 (24, 55)	45 (23, 55)
Age at reference date*, mean (range)	50 (27, 70)	50 (27, 69)
At-risk period, mean (range)	5 (1, 16)	5 (1, 16)
Counter-matched characteristics		
Radiation treatment (registry), *n* (%)		
No or unknown	415 (59)	290 (21)
Yes	293 (41)	1,109 (79)
Other characteristics		
First-degree family history of breast cancer, *n* (%)		
Adopted or family history unknown	11 (1)	26 (2)
No	472 (67)	1,088 (78)
Yes	225 (32)	285 (20)
Number of mammograms in year before reference date*, *n* (%)		
0	41 (6)	116 (8)
1	503 (71)	959 (69)
2	101 (14)	149 (11)
3+	19 (3)	20 (1)
Unknown	44 (6)	155 (11)
Histology of first breast cancer, *n* (%)		
Ductal and other	585 (82)	1,217 (87)
Lobular	90 (13)	131 (9)
Medullary	33 (5)	51 (4)
Stage of first breast cancer, *n* (%)		
Localized	503 (71)	911 (65)
Regional	205 (29)	488 (35)
Chemotherapy, *n* (%)		
No	386 (55)	629 (45)
Yes	322 (45)	770 (55)
Hormone therapy, *n* (%)		
No	511 (72)	909 (65)
Yes	197 (28)	488 (35)

*Reference date is date of contralateral breast cancer diagnosis for cases and corresponding date for controls.

Table 2. Risk factors for second primary CBC among WECARE subjects

Factor	Bilateral (*n*)	Unilateral (*n*)	Unadjusted (weighted), RR* (95% CI)	Adjusted (weighted), RR† (95% CI)
Age at menarche				
13+ y	367	782	1.00	1.00
<13 y	338	611	1.29 (1.04-1.60)	1.26 (1.01-1.58)
Menopausal status (as of reference date‡)				
Postmenopausal <45	209	455	1.00	1.00
Premenopausal	124	273	0.99 (0.71-1.36)	0.78 (0.55-1.10)
Postmenopausal 45+	374	665	1.32 (1.01-1.73)	1.20 (0.91-1.58)
Gravidity§				
Never pregnant	87	157	1.00	1.00
Incomplete pregnancies only	46	68	1.30 (0.78-2.18)	1.23 (0.73-2.09)
At least one full-term pregnancy	575	1,172	0.93 (0.68-1.29)	0.92 (0.66-1.28)
Age at first FTP (as of reference date‡)				
<20 y	77	170	1.00	1.00
20-24 y	236	461	1.28 (0.89-1.84)	1.13 (0.78-1.66)
25-29 y	159	363	1.15 (0.79-1.68)	0.96 (0.65-1.43)
Nulliparous or 30+ y	236	403	1.53 (1.06-2.21)	1.22 (0.77-1.92)
Trend *P* value				0.76
Number of FTPs (as of reference date‡)				
Nulliparous	133	225	1.00	1.00
1	121	204	1.17 (0.81-1.68)	1.14 (0.78-1.66)
2	270	545	0.92 (0.69-1.24)	0.92 (0.68-1.25)
3	128	263	0.72 (0.51-1.02)	0.73 (0.51-1.04)
4+	56	160	0.48 (0.31-0.75)	0.46 (0.29-0.72)
Trend *P* value				0.001
Breastfeeding (as of reference date‡)				
Never	336	608	1.00	1.00
Ever	372	789	0.79 (0.64-0.99)	0.82 (0.63-1.07)
Duration of breastfeeding (as of reference date‡)				
Never	336	608	1.00	1.00
1 to 3 mo	102	179	0.97 (0.71-1.34)	1.02 (0.71-1.45)
4 to 6 mo	94	211	0.79 (0.57-1.10)	0.75 (0.52-1.08)
7 to 23 mo	132	305	0.76 (0.57-1.02)	0.77 (0.55-1.08)
24+ mo	43	94	0.66 (0.43-1.03)	0.82 (0.50-1.34)
Trend *P* value				0.09

*Rate ratios are adjusted for the counter-matching sampling.
†Rate ratios are adjusted for the counter-matching sampling and for the following covariates: age at first diagnosis, age at menarche, age at menopause, number of full-term pregnancies, family history of breast cancer, histology of the first primary, stage of the first primary, first primary treatment history and radiation therapy.
‡Reference date is the date of contralateral breast cancer diagnosis for the cases and the corresponding date for controls.
§Rate ratios are adjusted for all the covariates listed above except for the number of full-term pregnancies.

compared with nulliparous women, those with three or more FTPs, all of which occurred before age 30, were observed to have significantly reduced risk of CBC (RR, 0.6; 95% CI, 0.4-0.9). However, women with FTPs after age 30 were not observed to have significantly reduced risk of CBC as compared with nulliparous women. We cannot rule out a protective effect from having children after age 30; nonetheless, this may be modest in comparison to that conferred by multiple FTPs occurring before age 30. Breastfeeding history was not significantly associated with risk of CBC (*P* trend = 0.09 for duration of breastfeeding). The results for effects of reproductive factors using date at first breast cancer diagnosis as the reference date for cases and controls were of similar magnitude as those presented, which include the at-risk period (data not shown). We also conducted age-stratified (<45, ≥45 years) analyses of CBC risk, examining the impact on CBC risk of age at first FTP, number of FTPs, and breastfeeding. The association between the reproductive characteristics and the risk of CBC did not differ by age (data not shown).

Discussion

In this study, we found that earlier menarche and lower parity were associated with risk of asynchronous CBC in women diagnosed with a first primary breast cancer before age 55 years. Age at first FTP, breastfeeding history, and menopausal status were not significantly associated with CBC risk.

Early menarche is considered a modest risk factor for first primary breast cancer (21). Two prior studies assessed risk of CBC in relation to age at menarche, and neither showed increased risk of CBC with menarche before age 13 years (4, 9). Combined with our results, these studies suggest that early age at menarche has, at most, a modest impact on CBC risk.

Parity is a well-established risk factor for breast cancer (21, 22). Our results showing a statistically significant decline in risk of CBC with increasing number of FTPs agree with those of the only population-based study to address this previously (9), where an adjusted RR of 0.62 for CBC risk associated with two or more FTPs was reported. It has been proposed that this observed protective effect for multiple FTPs is a result of the differentiation of breast stem cells which occurs during each FTP, leaving the cells less susceptible to carcinogenesis (23, 24). It is unclear whether the increased protection observed with each additional pregnancy is due to further differentiation of tissue with each succeeding pregnancy or changes in the hormonal milieu (25, 26) or a combination of factors. Our results further indicate that the protective effect of multiple FTPs is more pronounced when the pregnancies occur before age 30 years. Interestingly, however, an association between an early age at first FTP and CBC risk was not observed in the present analysis after adjusting for number of FTPs and other potential confounding factors. These findings suggest that the number of FTPs is a more important determinant of CBC risk than an early first FTP. In contrast, research examining the relative influences of parity and age at first FTP on risk of first primary breast cancer suggests these factors may be independent (12).

Breastfeeding has only a modest impact on risk of breast cancer overall after the impact of parity is considered (27). The findings of the present study agree with one previous study of breastfeeding and CBC, which also found no statistically significant association with CBC risk when number of pregnancies breast-fed was considered (9). Together, these results suggest that breastfeeding history is not an important predictor of CBC risk.

Our study has many strengths, including the large sample size, the population-based subject ascertainment, the abstraction of medical records to confirm a cancer-free interval for controls and treatment history for both cases and controls, and strict individual matching of the cases and controls. However, as with all case-control studies, our study has some potential limitations. First, although our study is the largest population-based case-control study conducted to date that included direct interviews of patients, we nevertheless had limited statistical power to detect modest relationships between age at first FTP and CBC or between duration of breastfeeding and CBC. Second, although we limited the potential for misclassification of metastases as second primary breast cancer by restricting this study to women with initial breast cancer diagnoses of localized and regional disease and specified a minimum interval of 1 year between the first and second diagnosis among the cases, the possibility of misclassification remains. Third, we conducted interviews with cases and controls, and so we were able to include a woman's history of reproductive events both before first breast cancer diagnosis and during her at-risk period before the cases' second primary diagnoses. However, by focusing on these reproductive events that are important for developing a first primary breast cancer, we may have missed some other factors that are predictors of a second primary. Lastly, we required that all of our cases and controls be alive so that we could obtain a blood sample. Thus, we cannot rule out the potential for a survival bias in our results. However, because we individually matched our controls to our cases on both age and year of first breast cancer diagnosis and restricted study eligibility to women whose breast cancer had not spread beyond regional lymph nodes at first diagnosis, this possibility is unlikely to differentially affect the cases and controls in our study.

In summary, our findings suggest that among women diagnosed with a first breast cancer before age 55 years, multiparity and late menarche are inversely associated with risk of CBC in a manner similar to the associations observed for first primary breast cancers. However, other reproductive factors basic to the epidemiology of first primary breast cancer such as early age at first FTP and breastfeeding do not seem to strongly influence CBC risk. Further research regarding populations at risk for developing CBC may be useful in developing strategies for primary and secondary prevention.

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