Reproductive factors and risk of contralateral breast cancer by \textit{BRCA1} and \textit{BRCA2} mutation status: results from the WECARE study

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Abstract

Objective Reproductive factors, such as early age at menarche, late age at menopause, and nulliparity are known risk factors for breast cancer. Previously, we reported these factors to be associated with risk of developing contralateral breast cancer (CBC). In this study, we evaluated the association between these factors and CBC risk among \textit{BRCA1} and \textit{BRCA2} (\textit{BRCA1/2}) mutation carriers and non-carriers.

Methods The WECARE Study is a population-based multi-center case–control study of 705 women with CBC (cases) and 1,397 women with unilateral breast cancer (controls). All participants were screened for \textit{BRCA1/2} mutations and 181 carriers were identified. Conditional logistic regression models were used to evaluate associations between reproductive factors and CBC for mutation carriers and non-carriers.

Results None of the associations between reproductive factors and CBC risk differed between mutation carriers and non-carriers. The increase in risk with younger age at menarche and decrease in risk in women with more than two full-term pregnancies seen in non-carriers were not significantly different in carriers (adjusted RR= 1.31, 95% CI 0.65–2.65 and 0.53, 95% CI 0.19–1.51, respectively). No significant associations between the other

The members of WECARE Study Collaborative Group are given in “Appendix”.

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reproductive factors and CBC risk were observed in mutation carriers or non-carriers.

**Conclusion** For two reproductive factors previously shown to be associated with CBC risk, we observed similar associations for BRCA1/2 carriers. This suggests that reproductive variables that affect CBC risk may have similar effects in mutation carriers and non-carriers.

**Keywords** Contralateral breast cancer · BRCA1 · BRCA2 · Reproductive factors

**Introduction**

The risk of cancer in the contralateral breast of women who survive their first breast cancer is higher than the risk of a first primary breast cancer in the general population [1]. Reproductive and hormonal factors are known to play an important role in the etiology of breast cancer. Previous studies, which have evaluated reproductive factors in contralateral breast cancer (CBC) [1–8], provide evidence that reproductive factors are associated with CBC risk. In a previous analysis of Women’s Environmental Cancer and Radiation Epidemiology (WECARE) Study data, older age at menarche and increasing number of births were statistically significantly associated with lower risk of CBC [2].

Women with mutations in BRCA1 and BRCA2 who have had breast cancer are also at an increased risk of developing asynchronous CBC [9, 10]. Reproductive factors, such as age at menarche [11, 12], menopausal status [12], parity [13–17], and breastfeeding [13, 15, 18, 19], have been evaluated as risk factors for first primary breast cancer in women who carry mutations in BRCA1 and BRCA2, with inconclusive results. The association between reproductive factors and CBC risk has not been studied in BRCA1 and BRCA2 mutation carriers to date. The association between reproductive factors and breast cancer has been shown to differ by tumor subtype [20–22]. In addition, tumor morphology and hormone receptor status have also been shown to differ between BRCA1 mutation carriers and non-carriers [23, 24]. Therefore, it is plausible that the associations between reproductive factors and CBC may differ in BRCA1 and BRCA2 mutation carriers and non-carriers.

The WECARE Study provides a unique opportunity for addressing this issue in that it is the first large scale population-based case control study of CBC and it includes BRCA1 and BRCA2 genotyping of all study participants. In this analysis, we examined commonly studied reproductive factors and CBC risk in BRCA1 and BRCA2 mutation carriers and non-carriers enrolled in the WECARE Study.

**Methods**

**Study population**

The WECARE study is a population-based multi-center study of asynchronous contralateral breast cancer (CBC). The study design has been described in detail previously [25]. Briefly, eligible cases were younger than 55 years when diagnosed between 1 January 1985 and 31 December 1999 with a first primary invasive breast cancer that had not spread beyond the regional lymph nodes; they were later diagnosed with a second primary in situ or invasive breast cancer in the contralateral breast at least 1 year after the first diagnosis. Control subjects were younger than age 55 when diagnosed on or after 1 January 1985 with a first primary breast cancer that had not spread beyond the regional lymph nodes. 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 1:2 counter-matched on registry-reported radiation exposure so that each triplet consisted of one radiation unexposed and two radiation exposed subjects [25]. In selecting controls, we created an “at risk” interval defined as the elapsed time (in days) between the matched case’s two breast cancer 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 and interview. Both cases and controls met the following criteria: (1) resided in the same reporting area within the “at risk” interval; (2) had no previous cancer diagnoses before or within the “at risk” interval; (3) were alive at time of contact; and (4) completed an interview and provided a blood sample. Controls had no prophylactic mastectomy of the contralateral breast before or within the “at risk” interval. Study participants were identified within five population-based tumor registries, covering the entire country of Denmark and in the US, the State of Iowa, Los Angeles County and the Orange County-San Diego regions of California, and 3 counties in Western Washington State.

Detailed information regarding the recruitment and response rates for the WECARE study has been previously described [2]. Briefly, 998 women with bilateral breast cancer and 2,112 women with unilateral breast cancer were eligible and approached for inclusion as cases and controls, respectively. A total of 705 (71%) CBC cases and 1,397 (66%) unilateral breast cancer controls participated in the study. We were able to recruit 694 counter-matched triplets, including 1 case and 2 controls where two members of each triplet were exposed to radiation based on registry records. In addition, 11 case–control pairs were included. Reasons for non-participation in the study include physician refusal (0.5% cases and 1% controls), interview refusal (27% cases and 31% controls), and blood draw refusal (3% cases and 3% controls).
The study protocol was approved by the Institutional Review Board at each study site and by the ethical committee system in Denmark. Informed consent was obtained from all study participants.

Data collection

Information on reproductive factors in the WECARE study was collected during a structured telephone interview as previously described [2]. The section on reproductive factors included information on age at menarche, menopausal status, number of pregnancies, age at first pregnancy, and lactation history. Reproductive factors were assessed as of the reference date (date of CBC diagnosis for cases and corresponding date for controls).

Family history information was obtained by self-report. Medical records, pathology reports, and hospital charts were used to collect detailed information on treatment (chemotherapy, hormonal therapy, and radiation therapy). Self-reported data were used to define treatment variables for the small number of women with missing medical record data. Information on tumor characteristics was collected from medical records or cancer registry records. Blood sample collection and DNA extraction were performed as previously described [25].

Genotyping of BRCA1 and BRCA2

BRCA1 and BRCA2 mutation screening has been previously described [26]. Briefly, denaturing high-performance liquid chromatography (DHPLC) was used to screen coding and flanking intronic regions for mutations or polymorphic variants. With the exception of the very prevalent polymorphic variants (occurring in >10% of samples) with clearly distinguishable chromatograms, all variant DHPLC results were confirmed by direct sequencing. Quality control procedures were implemented as previously described [27]. Mutation results for BRCA1 and BRCA2 were available for 2,103 of the 2,107 WECARE Study participants.

For this analysis, we focus on the variants that are considered to have a clearly deleterious effect based on current evidence. Deleterious variants are those with (1) changes known or predicted to truncate protein production including frameshift and nonsense variants, (2) splice site mutations occurring within 2 bp of an intron/exon boundary, and (3) missense changes that have been demonstrated to have a deleterious effect.

Statistical analysis

All statistical analyses were performed using SAS v.9.1 for Windows (SAS Institute, Cary, N.C.). We used conditional logistic regression to estimate multivariable rate ratios (RRs) with adjustment for reproductive factors (age at menarche, menopausal status, and number of pregnancies), age at diagnosis of first primary breast cancer, and other potential confounders (treatment, stage of first primary breast cancer, and family history). Because controls are independently sampled from failure time risk sets, the estimated parameters are rate ratios in the proportional hazards model for cohort data and standard likelihood methods apply [28]. BRCA1 and BRCA2 carrier/non-carrier (“carrier status”)-specific RRs for the associations between reproductive factors and CBC risk were estimated while accounting for the counter-matched case–control design. For example, to estimate carrier status-specific RRs for age at menarche (≥13 compared to <13 years) while adjusting for other reproductive factors, we fit a model that included two indicator variables for age at menarche, one for non-carriers and one for carriers, as well as a main effect variable for BRCA1/BRCA2 mutation-carrier status and adjustment variables for potential confounders. Heterogeneity of the age at menarche RRs by BRCA1/BRCA2 mutation-carrier status was evaluated using a likelihood ratio test comparing the carrier status-specific model to a model that included only the main effects for age of menarche and mutation-carrier status. The other reproductive factors were similarly evaluated. The counter-matching design was accommodated by including 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) to account for the sampling probability of the counter-matched case–control design; these weights were based on the number of radiation exposed and unexposed individuals within the sampled risk set [29, 30].

Results

We tested 2,103 women with breast cancer in the WE CARE Study and detected 181 with clearly deleterious mutations, including 109 in BRCA1 and 72 in BRCA2. Matched and counter-matched characteristics of the WE CARE study population stratified by BRCA1 and BRCA2 carrier status have been described in detail elsewhere [31]. BRCA1 and BRCA2 mutation carriers were younger at diagnosis of first breast cancer than non-carriers.

We evaluated associations between reproductive factors and CBC risk separately for BRCA1 and BRCA2 carriers as well as for all mutation carriers combined. We did not see convincing evidence that the results differed substantially for BRCA1 and BRCA2 carriers (data not shown); therefore, we combined the mutation carriers into one group to improve the precision of our RR estimates.

Table 1 shows associations between reproductive factors and CBC risk after adjustment for age at menarche,
menopausal status, number of pregnancies, age at first
diagnosis of breast cancer, treatment for first primary, and
stage of first primary. Family history was also considered
as a potential confounder, but inclusion of this variable did
not change any of the RRs by more than 10%. We present
only the multivariable adjusted RRs in Table 1 for
conciseness.

Tests for heterogeneity by carrier status do not support
any meaningful differences between carrier and non-carrier
risk estimates for any of the reproductive variables inves-
tigated (Table 1). We observed a statistically significantly
increased risk of CBC in women who reached menarche
before age 13 years and a decreasing risk of CBC with
increasing number of full-term pregnancies overall and in
non-carriers (p values for trend = 0.002 and 0.004,
respectively). Associations of a similar magnitude were
seen for carriers, although the results were not statistically
significant. We observed no significant associations
between CBC risk and menopausal status, age at first
pregnancy, or breastfeeding overall or stratified by carrier
status.

Discussion

In a previous analysis from the WECARE study [2],
reaching menarche before age 13 years was associated
with a modest but statistically significant increase in CBC

| Table 1 Association between reproductive factors and contralateral breast cancer by BRCA1 and BRCA2 mutation status |
|----------------|----------------|----------------|----------------|----------------|----------------|
|                | All cases and controls | BRCA1 and BRCA2 mutation carriers | Non-carriers |              |
|                | Cases | Controls | Adjusted | Cases | Controls | Adjusted | Cases | Controls | Adjusted | p value | heterogeneity |
| Age at menarche |        |          |          |        |          |          |        |          |          |         |             |
| ≥13 years      | 365  | 782     | 1.00 (Ref) | 58  | 46      | 1.00 (Ref) | 307  | 736     | 1.00 (Ref) | 0.93    |             |
| <13 years      | 337  | 610     | 1.28 (1.03–1.60) | 50  | 27      | 1.31 (0.65–2.65) | 287  | 583     | 1.27 (1.01–1.61) |         |             |
| Menopausal status (at reference date<sup>c</sup>) | | | | | | | | | | | |
| Postmenopausal | 208  | 455     | 1.00 (Ref) | 41  | 35      | 1.00 (Ref) | 167  | 420     | 1.00 (Ref) |         |             |
| <45 years      | 124  | 272     | 1.27 (0.97–1.67) | 36  | 20      | 1.54 (0.64–3.72) | 88   | 252     | 0.76 (0.52–1.11) |         |             |
| Postmenopausal | 372  | 665     | 1.00 (0.72–1.38) | 31  | 18      | 1.38 (0.56–3.36) | 341  | 647     | 1.28 (0.96–1.71) | 0.28    |             |
| Number of full-term pregnancies (at reference date<sup>d</sup>) | | | | | | | | | | | |
| Nulliparous    | 133  | 225     | 1.00 (Ref) | 21  | 13      | 1.00 (Ref) | 112  | 212     | 1.00 (Ref) |         |             |
| 1–2            | 388  | 749     | 0.97 (0.73–1.29) | 63  | 37      | 1.18 (0.49–2.88) | 325  | 712     | 0.94 (0.69–1.28) |         |             |
| >2             | 184  | 422     | 0.63 (0.45–0.87) | 24  | 23      | 0.53 (0.19–1.51) | 160  | 399     | 0.62 (0.44–0.88) | 0.66    |             |
| p value for trend | 0.002 |          | 0.21      |         |         |         | 0.004 |          |         | | |
| Age at first full-term pregnancy (at reference date<sup>c,d</sup>) | | | | | | | | | | | |
| <25 years      | 312  | 630     | 1.00 (Ref) | 52  | 32      | 1.00 (Ref) | 260  | 598     | 1.00 (Ref) |         |             |
| 25–29 years    | 158  | 363     | 0.86 (0.64–1.15) | 19  | 18      | 0.42 (0.16–1.10) | 139  | 345     | 1.00 (0.73–1.37) |         |             |
| 30+ years      | 102  | 178     | 1.19 (0.81–1.73) | 16  | 10      | 0.63 (0.20–2.05) | 86   | 168     | 1.29 (0.87–1.92) | 0.20    |             |
| p value for trend | 0.68 |          | 0.22      |         |         |         | 0.32 |          |         | | |
| Breastfeeding (at reference date<sup>c,d</sup>) | | | | | | | | | | | |
| Never          | 202  | 383     | 1.00 (Ref) | 31  | 18      | 1.00 (Ref) | 171  | 365     | 1.00 (Ref) |         |             |
| Ever           | 370  | 788     | 0.90 (0.67–1.20) | 56  | 42      | 0.57 (0.22–1.44) | 314  | 746     | 0.94 (0.69–1.28) | 0.30    |             |
| Breastfeeding duration (at reference date<sup>c,d</sup>) | | | | | | | | | | | |
| Never          | 202  | 383     | 1.00 (Ref) | 31  | 18      | 1.00 (Ref) | 171  | 365     | 1.00 (Ref) |         |             |
| 1–6 months     | 195  | 389     | 0.93 (0.67–1.28) | 18  | 20      | 0.41 (0.13–1.25) | 177  | 369     | 1.02 (0.73–1.43) |         |             |
| 7+ months      | 174  | 399     | 0.86 (0.62–1.21) | 37  | 22      | 0.68 (0.25–1.89) | 137  | 377     | 0.86 (0.60–1.23) | 0.26    |             |
| p value for trend | 0.39 |          | 0.56      |         |         |         | 0.40 |          |         | | |

<sup>a</sup> Ns may not sum to total due to missing data. Missing data: age at menarche (n = 9 non-carriers), menopausal status (n = 7 non-carriers), number of full-term pregnancies (n = 2 non-carriers), age at first pregnancy (n = 2 non-carriers), breastfeeding (n = 2 non-carriers), breastfeeding duration (n = 3, 2 non-carriers, 1 BRCA1 carrier)

<sup>b</sup> Adjusted for age at menarche, menopausal status, number of full-term pregnancies, age at first diagnosis of breast cancer, stage of first primary, and treatment of first primary (chemotherapy and hormonal therapy)

<sup>c</sup> The reference date is the date of contralateral breast cancer diagnosis for cases and the corresponding date for controls

<sup>d</sup> Includes only parous women
risk relative to later age at menarche (adjusted RR = 1.26, 95% CI 1.01–1.58) and an increasing number of full-term pregnancies was associated with decreasing CBC risk ($p$-trend = 0.001). We observed a similar but statistically non-significant increase in risk with younger age at menarche in mutation carriers and a statistically non-significant decrease in risk among women with more than two full-term pregnancies. Similar to our previous report of CBC overall [2], age at first full-term pregnancy, menopausal status, and breastfeeding were not associated with CBC in either mutation carriers or non-carriers. It is important to note that we are measuring the interaction between reproductive variables and carrier status on a multiplicative scale.

The lack of evidence supporting an interaction between carrier status and reproductive factors does not imply no increased risk for carriers; women who carry a mutation in \textit{BRCA1} or \textit{BRCA2} have an elevated baseline risk for CBC compared with non-carriers [26].

Reproductive factors are established risk factors for first primary breast cancer [32], with evidence that older age at menarche, younger age at menopause, young age at first pregnancy, and increased number of pregnancies are associated with a reduced risk of breast cancer. Increased duration of breastfeeding has also been associated with a decreased risk of primary breast cancer [33]. Studies suggest that pregnancy leads to an increased risk of developing primary breast cancer in the first years following childbirth followed by a subsequent decrease in risk [34].

Due to the heterogeneous nature of breast cancer, some risk factors may have stronger associations with particular subtypes of breast cancer. The risk of breast cancer associated with reproductive factors, most notably age at menarche and age at first birth, has been shown to differ by tumor histology [20] and hormone receptor status [21, 22]. Tumors from women with \textit{BRCA1} mutations frequently exhibit a basal epithelial phenotype typically associated with ER negative and erbB-2 (HER2/neu) negative breast cancer [23, 35, 36]. In addition, tumors in \textit{BRCA1} mutation carriers are more likely to be PR negative and p53 positive compared with tumors from non-carriers [24, 37]. The profile associated with \textit{BRCA2} mutations is not as distinct [24, 37, 38]; however, recent studies have found differences in morphology and hormone receptor status in \textit{BRCA2} mutation carriers and non-carriers [39, 40]. Based on these results, it is biologically plausible that the association between reproductive factors and risk of CBC may differ in \textit{BRCA1} and \textit{BRCA2} carriers and non-carriers.

The reproductive factors commonly associated with risk of first primary breast cancer have been evaluated in \textit{BRCA1} and \textit{BRCA2} mutation carriers to determine whether they influence risk in this subgroup. In matched case control study of \textit{BRCA1} and \textit{BRCA2} mutation carriers ($n = 1,311$ pairs), age at menarche was observed to be inversely associated with breast cancer in \textit{BRCA1} carriers but not \textit{BRCA2} carriers (OR = 0.46, 95% CI 0.30–0.69 and OR = 0.72, 95% CI 0.37–1.38 for $\geq 15$ years compared with $\leq 11$ years, respectively) [11]. In contrast, Chang-Claude et al. [12] found no association between age at menarche and risk of breast cancer in a study of 1,187 \textit{BRCA1} and 414 \textit{BRCA2} mutation carriers. In an analysis by the International BRCA1/2 Carrier Cohort Study, having four or more full-term pregnancies was associated with a reduced risk of breast cancer for \textit{BRCA1/2} carriers combined (OR = 0.65, 95% CI 0.42–1.00; $n = 1,601$ \textit{BRCA1/2} mutation carriers) [13]. However, an increasing number of births was not associated with risk of breast cancer in two studies [14, 15], while other studies showed that this association may differ by age at diagnosis [13, 16] or whether the mutation is in \textit{BRCA1} or \textit{BRCA2} [13].

Results for age at first birth have been mixed. In a study of Ashkenazi Jewish women, increasing age at first birth was associated with an increased risk of breast cancer in non-carriers, but a decreased risk was observed in carriers of \textit{BRCA1/2} founder mutations (RR = 0.65; 95% CI = 0.37–1.16 for each 5-year increment in age at first birth) [14]. Andrieu et al. [13] reported an increased risk of breast cancer with increased age at first birth among \textit{BRCA2} carriers (HR = 1.97, 95% CI = 0.67–5.81 for first birth $\geq 30$ years compared with first birth $<20$ years), while a decreased risk was observed among \textit{BRCA1} carriers (HR = 0.58, 95% CI = 0.36–0.94 for $\geq 30$ years compared with $<20$ years). Kotsopoulos et al. [17] reported no association between age at first birth and breast cancer risk in a large case–control study of \textit{BRCA1/2} mutation carriers (OR = 1.00 per year; 95% CI 0.98–1.03; $p$-trend = 0.67).

No consistent results have been reported for breastfeeding and breast cancer risk among \textit{BRCA1} and \textit{BRCA2} mutation carriers [13, 15, 18, 19]. In a case–control study of carriers of deleterious mutations in \textit{BRCA1} and \textit{BRCA2} ($n = 965$ matched pairs), Jernstrom et al. [18] reported a reduced risk of breast cancer among \textit{BRCA1} carriers who breast-fed for more than 1 year (OR = 0.55, 95% CI = 0.38–0.80), while no association was observed for \textit{BRCA2} carriers (OR = 0.95, 95% CI = 0.56–1.59). Andrieu et al. [13] did not report an association between breastfeeding and breast cancer among \textit{BRCA1/2} carriers (HR = 1.04, 95% CI 0.81–1.34 for ever vs. never).

To our knowledge, this is the first study to examine the association between CBC risk and reproductive factors in \textit{BRCA1} and \textit{BRCA2} carriers. Our data suggest that associations between reproductive factors and CBC in mutation carriers and non-carriers do not substantially differ. A previous study conducted among breast cancer families indicated that reproductive factors, including age at menarche, age at first full-term pregnancy, and nulliparity, did not differ between \textit{BRCA1} and \textit{BRCA2} carriers and non-carriers.
In addition, a study of breast cancer cases found no difference in median age at menarche, median age at first full-term pregnancy, and number of full-term pregnancies between BRCA mutation carriers and non-carriers [42].

This study has many strengths, including that it is population-based with complete risk factor information and BRCA1/2 genotyping for all participants. Nevertheless, there are also several limitations. In some of the subgroups, the number of mutation carriers limits the statistical power to detect small differences in the effect estimates between carriers and non-carriers. Some studies have suggested that risk may differ between BRCA1 carriers and BRCA2 carriers [11, 16]. The small number of mutation carriers in our study does not permit evaluation of associations for BRCA1 carriers separate from those of BRCA2 carriers.

Our genotyping strategy was not capable of identifying large deletions in BRCA1 and BRCA2, so it is possible that we have some individuals with undetected mutations in our study population. We may have additional misclassification because we have included individuals with unclassified variants in our non-carrier group. This is not likely to change our results substantially because the number of unclassified variants that are truly deleterious is likely to be small.

In a previous study [2], we observed significant associations between two reproductive factors (age at menarche and number of pregnancies) and CBC risk. In this analysis, we observed similar associations between these reproductive factors (age at menarche and number of pregnancies) and CBC risk. In this analysis, the number of mutation carriers limits the statistical power to detect small differences in the effect estimates between carriers and non-carriers. Some studies have suggested that risk may differ between BRCA1 carriers and BRCA2 carriers [11, 16]. The small number of mutation carriers in our study does not permit evaluation of associations for BRCA1 carriers separate from those of BRCA2 carriers.

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In a previous study [2], we observed significant associations between two reproductive factors (age at menarche and number of pregnancies) and CBC risk. In this analysis, we observed similar associations between these reproductive factors and CBC risk in BRCA1 and BRCA2 mutation carriers and non-carriers, although these results should be confirmed in future studies with a larger number of mutation carriers. These results suggest that the reproductive factors that affect CBC risk in non-carriers are unlikely to act substantially differently in BRCA1 and BRCA2 mutation carriers.

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Appendix

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References


