Title

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

Journal

Cancer Causes & Control, 21(6)

ISSN

0957-5243

Authors

Poynter, Jenny N

Langholz, Bryan

Largent, Joan

et al.

Publication Date

2010-06-01

DOI

10.1007/s10552-010-9510-0

Published in final edited form as:
Cancer Causes Control. 2010 June ; 21(6): 839–846. doi:10.1007/s10552-010-9510-0.

Reproductive factors and risk of contralateral breast cancer by *BRCA1* and *BRCA2* mutation status: results from the WECARE study

Jenny N. Poynter,
Department of Preventive Medicine, University of Southern, California, Los Angeles, CA, USA; Division of Pediatric Epidemiology and Clinical Research, University of Minnesota, 420 Delaware St SE, Moos 1-117, Minneapolis, MN 55455, USA

Bryan Langholz,
Department of Preventive Medicine, University of Southern, California, Los Angeles, CA, USA

Joan Largent,
Department of Epidemiology, University of California, Irvine, CA, USA

Lene Mellemkjær,
Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark

Leslie Bernstein,
Division of Cancer Etiology, Department of Population Sciences, City of Hope National Medical Center/Beckman Research Institute, Duarte, CA, USA

Kathleen E. Malone,
Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Charles F. Lynch,
Department of Epidemiology, University of Iowa, Iowa City, Iowa

Åke Borg,
Department of Oncology, Lund University, Lund, Sweden

Patrick Concannon,
Center for Public Health Genomics and Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, VA, USA

Sharon N. Teraoka,
Center for Public Health Genomics and Department of Biochemistry and Molecular Genetics, University of Virginia, Charlottesville, VA, USA

Shanyan Xue,
Department of Preventive Medicine, University of Southern, California, Los Angeles, CA, USA

Anh T. Diep,
Department of Preventive Medicine, University of Southern, California, Los Angeles, CA, USA

Therese Törngren,
Department of Oncology, Lund University, Lund, Sweden

poynt006@umn.edu .

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

Colin B. Begg,
Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Marinela Capanu,
Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Robert W. Haile,
Department of Preventive Medicine, University of Southern, California, Los Angeles, CA, USA

The WECARE Study Collaborative Group, and **Jonine L. Bernstein**
Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

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 *BRCA1* and *BRCA2* (*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 *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 RRs = 1.31, 95% CI 0.65–2.65 and 0.53, 95% CI 0.19–1.51, respectively). No significant associations between the other 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 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 WECARE Study and detected 181 with clearly deleterious mutations, including 109 in *BRCA1* and 72 in *BRCA2*. Matched and counter-matched characteristics of the WECARE 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 investigated (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 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 *BRCA1* or *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 *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 *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 *BRCA2* mutations is not as distinct [24,37,38]; however, recent studies have found differences in morphology and hormone receptor status in *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 *BRCA1* and *BRCA2* carriers and non-carriers.

The reproductive factors commonly associated with risk of first primary breast cancer have been evaluated in *BRCA1* and *BRCA2* mutation carriers to determine whether they influence risk in this subgroup. In matched case control study of *BRCA1* and *BRCA2* mutation carriers (*n* = 1,311 pairs), age at menarche was observed to be inversely associated with breast cancer in *BRCA1* carriers but not *BRCA2* carriers (OR = 0.46, 95% CI 0.30–0.69 and OR = 0.72, 95% CI 0.37–1.38 for ≥15 years compared with ≤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 *BRCA1* and 414 *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 *BRCA1/2* carriers combined (OR = 0.65, 95% CI 0.42–1.00; n = 1,601 *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 *BRCA1* or *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 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 *BRCA2* carriers (HR = 1.97, 95% CI = 0.67–5.81 for first birth ≥30 years compared with first birth <20 years), while a decreased risk was observed among *BRCA1* carriers (HR = 0.58, 95% CI = 0.36–0.94 for ≥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 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 breast-feeding and breast cancer risk among *BRCA1* and *BRCA2* mutation carriers [13,15,18,19]. In a case–control study of carriers of deleterious mutations in *BRCA1* and *BRCA2* (*n* = 965 matched pairs), Jernstrom et al. [18] reported a reduced risk of breast cancer among *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 *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 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 *BRCA1* and *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 *BRCA1* and *BRCA2* carriers and non-carriers [41]. 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 reproducstive 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.

Acknowledgments

This work was supported by National Cancer Institute (NCI) R01CA097397 and NCI U01CA083178. JNP was supported by NCI T32 CA009142.

Appendix

WECARE Study Collaborative Group

Memorial Sloan Kettering Cancer Center (New York, NY): Jonine L. Bernstein Ph.D. (WECARE Study P.I.), Colin B. Begg. Ph.D., Marinela Capanu Ph.D, Tracy M. Layne M.P.H., Anne S. Reiner M.P.H., Xiaolin Liang M.D.

City of Hope (Duarte, CA) (Los Angeles CA)**:** Leslie Bernstein Ph.D., Laura Donnelly-Allen (some work performed at University of Southern California)

Danish Cancer Society (Copenhagen, Denmark): Jørgen H. Olsen, M.D., D.M.Sc., Michael Andersson M.D., D.M.Sc.; Lisbeth Bertelsen M.D.Ph.D., Per Guldberg Ph.D., Lene Mellemkjær Ph.D

Fred Hutchinson Cancer Research Center (Seattle, WA): Kathleen E. Malone Ph.D., Noemi Epstein

International Epidemiology Institute (Rockville, MD) and Vanderbilt University (Nashville, TN): John D. Boice Jr. Sc.D.

Lund University (Lund, Sweden): Åke Borg Ph.D., Therese Törngren M.Sc, Lina Tellhed B.Sc.

Mount Sinai School of Medicine (New York, NY): Barry S. Rosenstein Ph.D., David P. Atencio Ph.D.

National Cancer Institute (Bethesda, MD): Daniela Seminara Ph.D., M.P.H

New York University (New York, NY): Roy E. Shore Ph.D., Dr.PH.

Norwegian Radium Hospital (Oslo, Norway): Anne-Lise Børresen-Dale Ph.D., Laila Jansen

University of California at Irvine (Irvine, CA): Hoda Anton-Culver Ph.D., Joan Largent Ph.D. M.P.H. (Co-Investigator)

University of Iowa (Iowa City, IA): Charles F. Lynch M.D., Ph.D., Jeanne DeWall M.A.

University of Southern California (Los Angeles, CA): Robert W. Haile Dr. P.H., Bryan M. Langholz Ph.D. (Co-Investigator), Duncan C. Thomas Ph.D. (Co-Investigator), Anh T. Diep (Co-Investigator), Shanyan Xue M.D., Nianmin Zhou, M.D, Evgenia Ter-Karapetova

University of Southern Maine (Portland, ME): W. Douglas Thompson Ph.D.

University of Texas, M.D. Anderson Cancer Center (Houston, TX): Marilyn Stovall Ph.D., Susan Smith M.P.H.

University of Virginia (Charlottesville, VA) (Some work performed at Benaroya Research Institute in Seattle, WA): Patrick Concannon, Ph.D., Sharon Teraoka, Ph.D., Eric R. Olson, Ph.D., Nirasha Ramchurren, Ph.D.

References

1. Chen Y, Thompson W, Semenciw R, Mao Y. Epidemiology of contralateral breast cancer. Cancer Epidemiol Biomarkers Prev 1999;8:855–861. [PubMed: 10548312]
2. Largent JA, Capanu M, Bernstein L, Langholz B, Mellemkjaer L, Malone KE, Begg CB, Haile RW, Lynch CF, Anton-Culver H, et al. Reproductive history and risk of second primary breast cancer: the WECARE study. Cancer Epidemiol Biomarkers Prev 2007;16:906–911. [PubMed: 17507614]
3. Storm HH, Andersson M, Boice JD Jr, Blettner M, Stovall M, Mouridsen HT, Dombernowsky P, Rose C, Jacobsen A, Pedersen M. Adjuvant radiotherapy and risk of contralateral breast cancer. J Natl Cancer Inst 1992;84:1245–1250. [PubMed: 1640483]
4. Vaittinen P, Hemminki K. Risk factors and age-incidence relationships for contralateral breast cancer. Int J Cancer 2000;88:998–1002. [PubMed: 11093827]
5. Li CI, Malone KE, Porter PL, Daling JR. Epidemiologic and molecular risk factors for contralateral breast cancer among young women. Br J Cancer 2003;89:513–518. [PubMed: 12888823]
6. Cook LS, White E, Schwartz SM, McKnight B, Daling JR, Weiss NS. A population-based study of contralateral breast cancer following a first primary breast cancer (Washington, United States). Cancer Causes Control 1996;7:382–390. [PubMed: 8734833]
7. Horn PL, Thompson WD. Risk of contralateral breast cancer: associations with factors related to initial breast cancer. Am J Epidemiol 1988;128:309–323. [PubMed: 3394698]
8. Bernstein JL, Thompson WD, Risch N, Holford TR. Risk factors predicting the incidence of second primary breast cancer among women diagnosed with a first primary breast cancer. Am J Epidemiol 1992;136:925–936. [PubMed: 1456269]

9. Metcalfe K, Lynch HT, Ghadirian P, Tung N, Olivotto I, Warner E, Olopade OI, Eisen A, Weber B, McLennan J, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22:2328–2335. [PubMed: 15197194]
10. Graeser MK, Engel C, Rhiem K, Gadzicki D, Bick U, Kast K, Froster UG, Schlehe B, Bechtold A, Arnold N, et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2009;27:5887–5892. [PubMed: 19858402]
11. Kotsopoulos J, Lubinski J, Lynch HT, Neuhausen SL, Ghadirian P, Isaacs C, Weber B, Kim-Sing C, Foulkes WD, Gershoni-Baruch R, et al. Age at menarche and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. Cancer Causes Control 2005;16:667–674. [PubMed: 16049805]
12. Chang-Claude J, Andrieu N, Rookus M, Brohet R, Antoniou AC, Peock S, Davidson R, Izatt L, Cole T, Nogues C, et al. Age at menarche and menopause and breast cancer risk in the international BRCA1/2 carrier cohort study. Cancer Epidemiol Biomarkers Prev 2007;16:740–746. [PubMed: 17416765]
13. Andrieu N, Goldgar DE, Easton DF, Rookus M, Brohet R, Antoniou AC, Peock S, Evans G, Eccles D, Douglas F, et al. Pregnancies, breast-feeding, and breast cancer risk in the international BRCA1/2 carrier cohort study (IBCCS). J Natl Cancer Inst 2006;98:535–544. [PubMed: 16622123]
14. Hartge P, Chatterjee N, Wacholder S, Brody LC, Tucker MA, Struewing JP. Breast cancer risk in Ashkenazi BRCA1/2 mutation carriers: effects of reproductive history. Epidemiology 2002;13:255–261. [PubMed: 11964925]
15. Tryggvadottir L, Olafsdottir EJ, Gudlaugsdottir S, Thorlacius S, Jonasson JG, Tulinius H, Eyfjord JE. BRCA2 mutation carriers, reproductive factors and breast cancer risk. Breast Cancer Res 2003;5:R121–R128. [PubMed: 12927042]
16. Cullinane CA, Lubinski J, Neuhausen SL, Ghadirian P, Lynch HT, Isaacs C, Weber B, Moller P, Offit K, Kim-Sing C, et al. Effect of pregnancy as a risk factor for breast cancer in BRCA1/BRCA2 mutation carriers. Int J Cancer 2005;117:988–991. [PubMed: 15986445]
17. Kotsopoulos J, Lubinski J, Lynch HT, Klijn J, Ghadirian P, Neuhausen SL, Kim-Sing C, Foulkes WD, Moller P, Isaacs C, et al. Age at first birth and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat 2007;105:221–228. [PubMed: 17245541]
18. Jernstrom H, Lubinski J, Lynch HT, Ghadirian P, Neuhausen S, Isaacs C, Weber BL, Horsman D, Rosen B, Foulkes WD, et al. Breast-feeding and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2004;96:1094–1098. [PubMed: 15265971]
19. Lee E, Ma H, McKean-Cowdin R, Van Den Berg D, Bernstein L, Henderson BE, Ursin G. Effect of reproductive factors and oral contraceptives on breast cancer risk in BRCA1/2 mutation carriers and noncarriers: results from a population-based study. Cancer Epidemiol Biomarkers Prev 2008;17:3170–3178. [PubMed: 18990759]
20. Reeves GK, Pirie K, Green J, Bull D, Beral V. Reproductive factors and specific histological types of breast cancer: prospective study and meta-analysis. Br J Cancer 2009;100:538–544. [PubMed: 19190634]
21. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomarkers Prev 2004;13:1558–1568. [PubMed: 15466970]
22. Ma H, Bernstein L, Pike MC, Ursin G. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. Breast Cancer Res 2006;8:R43. [PubMed: 16859501]
23. Foulkes WD, Stefansson IM, Chappuis PO, Begin LR, Goffin JR, Wong N, Trudel M, Akslen LA. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. J Natl Cancer Inst 2003;95:1482–1485. [PubMed: 14519755]
24. Lakhani SR, Van De Vijver MJ, Jacquemier J, Anderson TJ, Osin PP, McGuffog L, Easton DF. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. J Clin Oncol 2002;20:2310–2318. [PubMed: 11981002]
25. Bernstein JL, Langholz B, Haile RW, Bernstein L, Thomas DC, Stovall M, Malone KE, Lynch CF, Olsen JH, Anton-Culver H, et al. Study design: evaluating gene–environment interactions in the

etiology of breast cancer—the WECARE study. Breast Cancer Res 2004;6:R199–R214. [PubMed: 15084244]

26. Begg CB, Haile RW, Borg A, Malone KE, Concannon P, Thomas DC, Langholz B, Bernstein L, Olsen JH, Lynch CF, et al. Variation of breast cancer risk among BRCA1/2 carriers. JAMA 2008;299:194–201. [PubMed: 18182601]
27. Bernstein JL, Teraoka S, Haile RW, Borresen-Dale AL, Rosenstein BS, Gatti RA, Diep AT, Jansen L, Atencio DP, Olsen JH, et al. Designing and implementing quality control for multi-center screening of mutations in the ATM gene among women with breast cancer. Hum Mutat 2003;21:542–550. [PubMed: 12673797]
28. Borgan Ø , Goldstein L, Langholz B. Methods for the analysis of sampled cohort data in the cox proportional hazards model. Ann Stat 1995;23:1749–1778.
29. Langholz B, Borgan O. Counter matching: a stratified nested case–control sampling method. Biometrika 1995;82:69–79.
30. Langholz, B. Counter-matching. In: Armitage, P.; Colton, T., editors. Encyclopedia of biostatistics. 2nd edn.. Vol. 2. John Wiley and Sons; New York: 2005. p. 1248-1254.
31. Figueiredo JC, Haile RW, Bernstein L, Malone KE, Largent J, Langholz B, Lynch CF, Bertelsen L, Capanu M, Concannon P, et al. Oral contraceptives and postmenopausal hormones and risk of contralateral breast cancer among BRCA1 and BRCA2 mutation carriers and noncarriers: the WECARE Study. Breast Cancer Res Treat 2009;120:175–183. [PubMed: 19597986]
32. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev 1993;15:36–47. [PubMed: 8405211]
33. Kelsey JL, Gammon MD, John EM. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet 2002;360:187–195. [PubMed: 12133652]
34. Lambe M, Hsieh C, Trichopoulos D, Ekbom A, Pavia M, Adami HO. Transient increase in the risk of breast cancer after giving birth. N Engl J Med 1994;331:5–9. [PubMed: 8202106]
35. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, Deng S, Johnsen H, Pesich R, Geisler S, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 2003;100:8418–8423. [PubMed: 12829800]
36. Lakhani SR, Reis-Filho JS, Fulford L, Penault-Llorca F, van der Vijver M, Parry S, Bishop T, Benitez J, Rivas C, Bignon YJ, et al. Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. Clin Cancer Res 2005;11:5175–5180. [PubMed: 16033833]
37. Eerola H, Heikkila P, Tamminen A, Aittomaki K, Blomqvist C, Nevanlinna H. Histopathological features of breast tumours in BRCA1, BRCA2 and mutation-negative breast cancer families. Breast Cancer Res 2005;7:R93–R100. [PubMed: 15642173]
38. Armes JE, Trute L, White D, Southey MC, Hammet F, Tesoriero A, Hutchins AM, Dite GS, McCredie MR, Giles GG, et al. Distinct molecular pathogeneses of early-onset breast cancers in BRCA1 and BRCA2 mutation carriers: a population-based study. Cancer Res 1999;59:2011–2017. [PubMed: 10213514]
39. Bane AL, Beck JC, Bleiweiss I, Buys SS, Catalano E, Daly MB, Giles G, Godwin AK, Hibshoosh H, Hopper JL, et al. BRCA2 mutation-associated breast cancers exhibit a distinguishing phenotype based on morphology and molecular profiles from tissue microarrays. Am J Surg Pathol 2007;31:121–128. [PubMed: 17197928]
40. Brekelmans CT, Tilanus-Linthorst MM, Seynaeve C, vd Ouweland A, Menke-Pluymers MB, Bartels CC, Kriege M, van Geel AN, Burger CW, Eggermont AM, et al. Tumour characteristics, survival and prognostic factors of hereditary breast cancer from BRCA2-, BRCA1- and non-BRCA1/2 families as compared to sporadic breast cancer cases. Eur J Cancer 2007;43:867–876. [PubMed: 17307353]
41. Jernstrom HC, Johannsson OT, Loman N, Borg A, Olsson H. Reproductive factors in hereditary breast cancer. Breast Cancer Res Treat 1999;58:295–301. [PubMed: 10718491]
42. Atchley DP, Albarracin CT, Lopez A, Valero V, Amos CI, Gonzalez-Angulo AM, Hortobagyi GN, Arun BK. Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. J Clin Oncol 2008;26:4282–4288. [PubMed: 18779615]

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[a]	Controls[a]	Adjusted[b] RR (95% CI)	Cases[a]	Controls[a]	Adjusted[b] RR (95% CI)	Cases[a]	Controls[a]	Adjusted[b] RR (95% CI)	*p* value heterogeneity
Age at menarche										
≥13 years	365	782	1.00 (Ref)	58	46	1.00 (Ref)	307	736	1.00 (Ref)	
<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)	0.93
Menopausal status (at reference date[c])										
Postmenopausal <45 years	208	455	1.00 (Ref)	41	35	1.00 (Ref)	167	420	1.00 (Ref)	
Premenopausal	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 ≥45 years	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[c])										
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[c,d])										
<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[c,d])										
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[c,d])										
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	

[a] 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)

[b] 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)

[c] The reference date is the date of contralateral breast cancer diagnosis for cases and the corresponding date for controls

[d] Includes only parous women