

Age at first birth and the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers

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Abstract An early age at first full-term birth is associated with a reduction in the subsequent development of breast cancer among women in the general population. A similar effect has not yet been

reported among women who carry an inherited *BRCA1* or *BRCA2* mutation. We conducted a matched case–control study on 1816 pairs of women with a *BRCA1* ($n = 1405$) or *BRCA2* ($n = 411$) mutation in an attempt to elucidate the relationship between age at first full-term pregnancy and the risk of developing breast cancer. Information about the age at first childbirth and other pregnancy-related variables was derived from a questionnaire administered to women during the course of genetic counselling. There was no difference in the mean age at first full-term birth in the cases and controls (24.9 years vs. 24.8 years; $P = 0.81$, respectively). Compared to women whose first child was born at or before 18 years of age, a later age at first full-term birth did not influence the risk of developing breast cancer (OR = 1.00 per year; 95% CI 0.98–1.03; P -trend = 0.67). Stratification by mutation status did not affect the results. These findings suggest that an early first full-term birth does not confer protection against breast cancer in *BRCA* mutation carriers.

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Nonetheless, *BRCA* mutation carriers opting for a prophylactic oophorectomy as a breast and/or ovarian cancer risk-reducing strategy should complete child-bearing prior to age 40 when this prevention modality is most effective.

Keywords *BRCA1* · *BRCA2* · Age at first birth · Breast cancer · Case–control study

Introduction

A woman's reproductive history is an important determinant of her breast cancer risk [1]. Factors that protect against breast cancer in the general population include a late age of onset of menarche, multiparity, breastfeeding, and an early age at menopause [2, 3]. Of particular importance is the age at which a woman completes her first full-term pregnancy [4, 5]. An early age at first childbirth (i.e., before the age of 20) has been reported to reduce a women's risk of developing breast cancer by up to one-half [4]; whereas, a late age at first childbirth (e.g., at age 30 or older) increases her risk.

Various studies have shown that the risk associated with a late first-term pregnancy may be as great as, or higher, than the risk associated with nulliparity [6, 7].

Women who inherit a deleterious mutation in either of the two breast cancer susceptibility genes, *BRCA1* or *BRCA2*, face a lifetime risk of breast cancer of approximately 80% [8, 9]. The incomplete penetrance of *BRCA1* and *BRCA2* suggests that there may be the potential to modify risk [10–12]. To date, various hormonal and reproductive factors have been found to influence a woman's susceptibility to *BRCA*-associated breast cancer; these implicate an important role of estrogen-signaling (reviewed in [13]). Various groups have investigated the roles of reproductive and menstrual factors on the risk of developing breast cancer in *BRCA* mutation carriers, with inconsistent results (reviewed in [13]). However, the role of age at first-full term birth in the etiology of hereditary breast cancer has not yet been elucidated [14–19]. We conducted a case–control study on a sample of *BRCA1* and *BRCA2* mutation carriers in an attempt to clarify the relationship between age at first full-term pregnancy and the subsequent risk of developing breast cancer.

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Materials and methods

Study population and design

Eligible study subjects included living women who were identified at any one of 54 participating centers in 11 countries. These women were participants in ongoing research or clinical research protocols at the host institutions. All study subjects (with the exception of those from the University of Utah and the University of California Irvine) received counselling and provided written informed consent for genetic testing.

The institutional review boards of the host institutions approved the study. In most cases, testing was initially offered to women who had been affected with breast or ovarian cancer. When a *BRCA1* or *BRCA2* mutation was identified in a proband or her relative, genetic testing was offered to other at-risk individuals in the family. Mutation detection was performed using a range of techniques, but all nucleotide sequences were confirmed by direct sequencing of DNA. A woman was eligible for the current study when the molecular analysis established that she was a carrier of a deleterious mutation in the *BRCA1* or *BRCA2* gene. Most (>95%) of the mutations identified in the study subjects were either nonsense mutations, deletions, insertions, or small frameshifts resulting in a premature termination of protein translation.

Information was available on cancer and reproductive histories for a total of 7,243 women who carried a *BRCA1* or *BRCA2* mutation. Case subjects were study subjects with a diagnosis of invasive breast cancer. Control subjects were women who never had breast cancer and who were also carriers of a mutation in *BRCA1* or *BRCA2*. Potential subjects were excluded if

they had been diagnosed with ovarian (62 women) or other cancer (450 women) prior to the year of breast cancer diagnosis of the case, or if information about pregnancy-related information was incomplete (362 women). Three potential case subjects were excluded due to missing information regarding the year of breast cancer diagnosis. After exclusions, there were a total of 6,366 eligible women, including 2,904 women with breast cancer (potential case subjects) and 3,462 women without breast cancer (potential controls).

Data collection

Case and controls subjects completed a questionnaire that asked for information regarding family history, reproductive and medical histories, and selected lifestyle factors including smoking and the use of oral contraceptives. Questionnaires were administered at the individual centers at the time of a clinic appointment or at their home at a later date. The participants were asked if they had ever been pregnant and were asked to consider all pregnancies, in order, from first to last and provide the year and outcome of each pregnancy. Additional variables of interest included information on residence and ethnic group.

Statistical analyses

A matched case–control analysis was performed to evaluate the association between the age at first full-term pregnancy and risk of breast cancer. A single control subject was selected for each case subject, matched according to mutation in the same gene (*BRCA1* or *BRCA2*), year of birth (within 1 year), country of residence and a diagnosis of ovarian cancer

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Table 1 Characteristics of case and control subjects

| Variable | Control subjects, <i>N</i> = 1,853 | Case subjects, <i>N</i> = 1,853 | <i>P</i> ^a |
|--|---------------------------------------|------------------------------------|-----------------------|
| Current age, mean (SD) ^b | 47.2 (10.4) | 47.1 (10.1) | 0.86 |
| Date of birth, mean year (SD) | 1953.6 (10.4) | 1953.4 (10.7) | 0.56 |
| Breast cancer, mean age of diagnosis (SD) | NA | 39.7 (8.0) | |
| Mutation, <i>N</i> (%) | | | |
| BRCA1 | 1405 (77.4) | 1405 (77.4) | |
| BRCA2 | 411 (22.6) | 411 (22.6) | |
| Age at menarche, mean (SD) | 13.0 (1.5) | 12.9 (1.5) | 0.005 |
| Breastfeeding, <i>N</i> (%) | | | |
| Never | 647 (39.6) | 676 (42.7) | |
| Ever | 987 (60.4) | 909 (57.4) | 0.08 |
| Missing | 182 | 231 | |
| Oral contraceptive use ^c , <i>N</i> (%) | | | |
| Ever | 1138 (63.1) | 1146 (64.2) | 0.50 |
| Ovarian cancer, <i>N</i> (%) | 185 (10.2) | 189 (10.2) | |
| Oophorectomy ^d , <i>N</i> (%) | | | |
| Yes | 85 (4.7) | 48 (2.7) | 0.001 |
| Smoking | | | |
| Ever | 756 (43.1) | 761 (43.4) | 0.88 |
| Country of residence, <i>N</i> (%) ^e | | | |
| United States | 643 (20.0) | 643 (20.0) | |
| Canada | 489 (26.4) | 489 (26.4) | |
| Poland | 372 (20.1) | 372 (20.1) | |
| Israel | 89 (4.8) | 89 (4.8) | |
| Netherlands | 84 (4.5) | 84 (4.5) | |
| Norway | 59 (3.2) | 59 (3.2) | |
| Italy | 32 (1.7) | 32 (1.7) | |
| Austria | 28 (1.5) | 28 (1.5) | |
| Sweden | 10 (0.5) | 10 (0.5) | |
| United Kingdom | 9 (0.5) | 9 (0.5) | |
| France | 1 (0.1) | 1 (0.1) | |
| Ethnicity, <i>N</i> (%) | | | |
| Other white | 1137 (68.1) | 1237 (68.1) | |
| Jewish | 415 (22.9) | 390 (21.5) | |
| French-Canadian | 137 (7.5) | 143 (7.9) | |
| Other | 27 (1.5) | 46 (2.5) | 0.12 |

^a All *P* values are univariate and were derived using the Student's *t*-test for continuous variables and the χ^2 -test for categorical variables

^b SD = standard deviation

^c There data missing for 12 control and 30 cases

^d There data missing for 7 control and 16 cases

^e Country of residence at time of testing

(the ovarian cancer diagnosis had to have occurred after the year of breast cancer diagnosis of the matched case subject). In addition, bilateral mastectomy had to have occurred after the year of breast cancer diagnosis of the matched case subject. A total of 1,816 matched case–control pairs was generated, including 1,405 pairs with *BRCA1* mutations and 411 pairs with *BRCA2* mutations. The mean age at first full-term pregnancy for parous woman was compared between the case subjects and control subjects using the Student's *t*-test. This test statistic was also used for all other continuous variables. The χ^2 -test was used to test for differences in categorical variables and to compare the proportion of case and control subjects in each age at first full-term birth category. The multivariate odds ratios (OR), 95% confidence intervals (CI) and tests for linear trend were estimated by use of conditional logistic regression. Women with a first birth at or before the age of 18 were used as the referent group. A multivariate analysis was carried out to control for the potential confounding effects of age at menarche, oral contraceptive use

(ever/never), prophylactic oophorectomy (yes/no), parity (one, two, three, four or more births), breast-feeding (ever/never) and ethnicity (Caucasian, French–Canadian, Jewish, and other). Parity included both live- and still-born births, and twin or triplet pregnancies were coded as one birth. All statistical tests were two-sided. All analyses were performed using the SAS statistical package, version 8.1 (SAS Institute, Cary, NC).

Results

Case and control subjects were similar with respect to age, oral contraceptive use, and parity (Table 1). The average age at menarche of the case subjects was significantly earlier than that of the control subjects (12.9 vs. 13.0 years; *P* = 0.005) and cases were less likely to have had an oophorectomy than controls (2.7% vs. 4.7%; *P* = 0.001). Breastfeeding was less common among the case subjects (57.4% vs. 60.4%),

Table 2 Comparison of parity and age at first full-term birth between case and control subjects

| Variable | Control subjects, N = 1,853 | Case subjects, N = 1,853 | <i>P</i> ^a |
|---|--------------------------------|-----------------------------|-----------------------|
| Parity ^b , N (%) | | | |
| 0 | 363 (20.0) | 349 (19.2) | |
| 1 | 275 (15.1) | 282 (15.5) | |
| 2 | 668 (36.8) | 694 (38.2) | |
| 3 | 305 (16.8) | 334 (18.4) | |
| 4 or more | 205 (11.3) | 157 (8.7) | 0.07 |
| Parity, mean (SD) ^c | 1.93 (1.5) | 1.88 (1.4) | 0.36 |
| Age at first full-term birth, mean (range) | | | |
| All | 24.83 (15–42) | 24.87 (14–43) | 0.81 |
| <i>BRCA1</i> | 24.60 (15–42) | 24.73(15–43) | 0.49 |
| <i>BRCA2</i> | 25.65 (16–41) | 25.32 (14–41) | 0.37 |
| OVCA ^d | 23.96 (17–40) | 24.31 (17–43) | 0.44 |
| No OVCA | 24.93 (15–42) | 24.94 (14–42) | 1.00 |
| Distribution of cases and controls by age at first full-term birth, N (%) | | | |
| No pregnancies | 363 (20.0) | 349 (19.2) | |
| Age at first full-term birth | | | |
| ≤18 | 68 (3.7) | 72 (4.0) | |
| 19 | 67 (3.7) | 78 (4.3) | |
| 20 | 94 (5.2) | 97 (5.3) | |
| 21 | 129 (7.1) | 124 (6.8) | |
| 22 | 134 (7.4) | 129 (7.1) | |
| 23 | 142 (7.8) | 143 (7.9) | |
| 24 | 136 (7.5) | 128 (7.1) | |
| 25 | 126 (6.9) | 108 (6.0) | |
| 26 | 103 (5.7) | 107 (5.9) | |
| 27 | 91 (5.0) | 86 (4.7) | |
| 28 | 74 (4.1) | 89 (4.9) | |
| 29 | 75 (4.1) | 78 (4.3) | |
| 30 | 49 (2.7) | 60 (3.3) | |
| 31 | 32 (1.8) | 48 (2.6) | |
| 32 | 38 (2.1) | 33 (1.8) | |
| 33–34 | 51 (2.8) | 37 (2.0) | |
| ≥35 | 44 (2.4) | 50 (2.8) | 0.13 ^e |

^a All *P* values are univariate and were derived using the Student's *t*-test for continuous variables and the chi-square test for categorical variables

^b Parity includes live born and still born, and was included only in analysis if birth was one calendar year before the age of diagnosis of the matched case

^c SD = standard deviation

^d OVCA = ovarian cancer

^e This *P*-value was derived using the frequency test. The *P*-values following stratification by *BRCA* mutation status was 0.85 and is 0.56 for *BRCA1* and *BRCA2* carriers, respectively

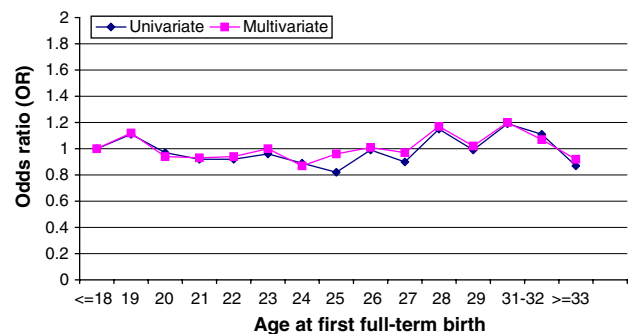
although this difference did not reach statistical significance (*P* = 0.08).

Among parous women, there was no difference in the mean age at first full-term birth in the entire study population (24.9 vs. 24.8; *P* = 0.81 for cases and controls, respectively). The mean age at first full-term birth did not differ between *BRCA1* case and control subjects (24.7 vs. 24.6; *P* = 0.49), nor between *BRCA2* case and control subjects (25.3 vs. 25.7; *P* = 0.37). The

Table 3 Age at first full-term pregnancy and risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers

| Age at first full-term birth | Univariate OR (95% CI) | <i>P</i> | Multivariate OR ^a (95% CI) | <i>P</i> |
|------------------------------|------------------------|----------|---------------------------------------|----------|
| ≤18 | 1 | | 1 | |
| 19 | 1.12 (0.70–1.79) | 0.65 | 1.12 (0.69–1.82) | 0.65 |
| 20 | 0.97 (0.62–1.50) | 0.88 | 0.94 (0.60–1.48) | 0.78 |
| 21 | 0.92 (0.60–1.40) | 0.69 | 0.93 (0.61–1.44) | 0.75 |
| 22 | 0.92 (0.61–1.38) | 0.67 | 0.94 (0.61–1.43) | 0.76 |
| 23 | 0.96 (0.63–1.45) | 0.84 | 1.00 (0.65–1.54) | 1.00 |
| 24 | 0.89 (0.59–1.34) | 0.58 | 0.87 (0.57–1.33) | 0.53 |
| 25 | 0.82 (0.54–1.24) | 0.34 | 0.90 (0.58–1.39) | 0.64 |
| 26 | 0.99 (0.65–1.53) | 0.98 | 1.01 (0.65–1.57) | 0.97 |
| 27 | 0.90 (0.57–1.42) | 0.66 | 0.97 (0.60–1.56) | 0.90 |
| 28 | 1.15 (0.73–1.83) | 0.55 | 1.17 (0.72–1.91) | 0.52 |
| 29 | 0.99 (0.62–1.57) | 0.96 | 1.02 (0.63–1.66) | 0.94 |
| 30 | 1.19 (0.71–1.98) | 0.51 | 1.20 (0.70–2.05) | 0.50 |
| 31–32 | 1.11 (0.69–1.77) | 0.67 | 1.07 (0.66–1.75) | 0.79 |
| ≥33 | 0.87 (0.56–1.37) | 0.55 | 0.92 (0.57–1.50) | 0.75 |
| Trend | 1.00 (0.98–1.02) | 0.82 | 1.01 (0.98–1.03) | 0.67 |

^a All ORs were derived using multivariate conditional logistic regression and were adjusted for age at menarche (continuous), OC use (ever/never), oophorectomy (yes/no), parity (zero, one, two, three, four and four or more births), breastfeeding (ever/never), and ethnicity (other white, French-Canadian, Jewish, and other)

**Fig. 1** Age at first full-term birth and risk of breast cancer in *BRCA* mutation carriers

proportions of cases and controls with a first-full term birth in each age category were similar (*P* = 0.13; frequency test) (Table 2).

When compared to women whose first child was born at or before 18 years of age, an increasing age at first full-term birth did not influence the risk of developing breast cancer (OR = 1.00 per year; 95% CI 0.98–1.02; *P*-trend = 0.82) (Table 3). Adjusting for the covariates in the multivariate model did not modify the results (Table 3 and Fig. 1). We also examined the association with age at first full-term pregnancy and breast cancer risk following stratification by mutation status (*BRCA1* vs. *BRCA2*), with similar results (data

not shown). The univariate and multivariate OR's associated with each first-full term birth age category are depicted graphically in Fig. 1.

Discussion

Our findings suggest that an early full-term birth does not confer protection against breast cancer in *BRCA* mutation carriers. We found that the risk of breast cancer did not increase with an increasing age of first pregnancy (OR = 1.00 per year; 95% CI 0.98–1.03; *P*-trend = 0.67). It appears that the protective role of an early age at first childbirth, which is seen in the general population, is not an important risk factor for genetically predisposed women. Our findings are in agreement with other smaller studies that have reported that an earlier age at first full-term pregnancy does not confer protection against *BRCA*-associated breast cancers [14, 15, 17, 18]. However, two studies have shown that the age at first full-term pregnancy does influence *BRCA*-associated breast cancer. Rebbeck et al. observed a threefold increase in *BRCA*-associated breast cancer risk among nulliparous mutation carriers or whose age at first live birth occurred after 30 (OR = 3.06; 95% CI 1.52–6.16) [16]. It should be mentioned that approximately one third of the participants in the Rebbeck et al. study were also included in this study. In a recent international study of 1601 of *BRCA* carriers, the authors reported a significant effect in the opposite direction [19]. Compared with those who had a first birth before the age of 20, a late age at first childbirth (at or after the age of 30) among *BRCA1* mutation carriers was associated with a hazard ratio of 0.58 (95% CI 0.36–0.94; *P*-trend = 0.03).

In summary, it appears that the age of a first full-term birth does not affect a woman's subsequent risk of developing breast cancer. This observation suggests that factors that predict risk in the general population

may not be directly applicable to genetically predisposed women. Table 4 summarizes the reproductive risk factors and their respective odds ratios in *BRCA* mutation carriers from previous studies derived from this cohort of women. It is perhaps surprising that a later age at menarche and oophorectomy confer protection, but that an early age at first full-term birth does not. However, the role of pregnancy in the etiology of *BRCA*-breast cancer is not clear. A recent study by Cullinane et al. showed that a protective effect of multiparity only present among *BRCA1* mutation carriers with four or more children, but that increasing parity was a risk factor for *BRCA2*-associated breast cancer [20]. Other reproductive factors (i.e. age at menarche and breastfeeding) appear to play a less important role in the etiology of *BRCA2*- than *BRCA1*-associated carcinogenesis [21, 22].

Studies suggest an important role of the *BRCA1* and *BRCA2* proteins in mammary cell differentiation and proliferation [23, 24]. Rajan et al. have shown that mRNA expression of both *BRCA1* and *BRCA2* are at their maximum in proliferating cells in mice undergoing puberty- or pregnancy-induced differentiation and that the spatial and temporal patterns of expressions are similar [24]. However, in response to the ovarian hormones 17 β -estradiol and progesterone, there was a significantly greater up-regulation of *BRCA1* than *BRCA2* mRNA in the breast, demonstrating different responses of the two genes to sex hormones [24]. Levels of *BRCA1* and *BRCA2* mRNA are also elevated in the mammary glands of parous mice indicating their role as markers of breast differentiation [24, 25]. The *BRCA* proteins interact with Stat5a, a mammary gland transcription factor that is stimulated by prolactin at the end of pregnancy, and are involved in the growth and terminal differentiation of breast epithelial cells [26]. *BRCA1* has also been shown to suppress estrogen-mediated breast cell proliferation, in vitro [27].

The breasts of nulliparous women are predominantly composed of undifferentiated (type 1) lobules,

Table 4 Summary of various reproductive factors and the risk of breast cancer in *BRCA* mutation carriers from this same cohort of women

| Reproductive factor | <i>BRCA1</i> | | <i>BRCA2</i> | | Reference |
|--|------------------|----------|------------------|----------|-----------|
| | OR (95%CI) | <i>P</i> | OR (95%CI) | <i>P</i> | |
| Age at menarche— ≥ 15 years vs. ≤ 11 years | 0.46 (0.30–0.69) | 0.0002 | 0.72 (0.37–1.38) | 0.32 | [22] |
| Parity vs. nulliparity | 0.94 (0.50–1.19) | 0.62 | 1.37 (0.93–2.03) | 0.12 | [20] |
| Increasing parity—trend per childbirth | 0.94 (0.86–1.02) | 0.12 | 1.15 (1.00–1.33) | 0.05 | [20] |
| Breastfeeding— >1 year vs. no breastfeeding | 0.55 (0.38–0.80) | 0.001 | 0.95 (0.66–1.59) | 0.83 | [21] |
| Oophorectomy— \leq age 40 vs. no oophorectomy | 0.36 (0.20–0.64) | 0.0005 | 0.69 (0.25–1.95) | 0.49 | [33] |

NA, Not applicable

which have a high proliferative index and a high concentration of steroid hormone receptors [28]. They are believed to be more susceptible to carcinogenic insult and are considered to be the sites of origin of breast carcinomas. The parity-induced protective effect is believed to be due to the hormone-induced differentiation that occurs in the lobules of mammary epithelial cells turning them into type 2 and predominantly, type 3 lobules, making them less susceptible to carcinogens [28–30]. Thus, an early age at first childbirth should result in a differentiated state and reduced risk of developing breast cancer.

Russo et al. have reported that the developmental pattern of breast tissue from parous women with a family history of breast cancer or a *BRCA1* mutation was similar to that of nulliparous women, suggesting a functional role of the *BRCA1* gene in the branching pattern of the breast during lobular development associated with pregnancy [31]. Lack of *BRCA1* results in no, or poor, differentiation and development of the breast. Others have also demonstrated abnormal mammary development in response to pregnancy using a mouse model with a tissue-specific *BRCA1* mutation [32]. As suggested by Russo et al., it may be that pregnancy does not induce the expected terminal differentiation and reduction of the at-risk population of breast cells in *BRCA1* mutation carriers [29] and thus, does not confer protection against the development *BRCA1*-associated breast cancer. This hypothesis is consistent with our observation. The effect of pregnancy on the lobular architecture of *BRCA2* mutation carriers has not yet been reported.

Ours was a case–control study and we used self-reported historical data. However, personal recall of age at first birth is without a doubt accurate for most women. Strengths of our study included a large sample of known *BRCA* mutation carriers. We included 1,816 matched pairs and our matching criteria ensured that the case and control subjects were similar with respect to year of birth, mutation, and country of residence. All potential confounding factors were accounted for in the multivariate model. Previous studies have been limited by their small sample sizes as well as the inclusion of specific subgroups of women (i.e., women of Ashkenazi Jewish ethnicity or women with the Icelandic *BRCA2* founder mutation).

Here we report no effect of age at first full-term pregnancy on the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers as a whole. There appears to be no compelling reason for *BRCA1* or *BRCA2* mutation carriers to start their childbearing early with respect to breast cancer; however, women who have a birth should be encouraged to breastfeed [21]. Never-

theless, those women considering a prophylactic oophorectomy as a means to protect against the development ovarian cancer should aim to complete their childbearing prior to the age of 40 when the risk for ovarian cancer starts to rise [33]. These data offer valuable information for use in the counselling and clinical management of *BRCA* mutation carriers of childbearing age.

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