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Pregnancies, breastfeeding, and breast cancer risk in the International BRCA1/2 Carrier Cohort Study (IBCCS)

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ABSTRACT

Background: Multiparity, young age at first childbirth, and breastfeeding are associated with a reduced risk of breast cancer in the general population. The breast cancer predisposition gene, BRCA1, has been shown to have a central role in regulating normal cell differentiation. Reproductive factors may thus have an influence on breast cancer risk in BRCA1/2 carriers since mammary gland cells undergo cell division and differentiation during pregnancy.

Methods: We performed a retrospective cohort study of 1601 women who carried a mutation in BRCA1 or BRCA2. Information on reproductive factors was obtained from a questionnaire completed subsequent to genetic counseling. At censoring, 853 subjects were affected with breast cancer. Data analysis was performed using a weighted cohort approach. All statistical tests were two-sided. **Results:** There was no statistically significant difference in the risk of breast cancer between parous and nulliparous women. Among parous women, an increasing number of full-term pregnancies was associated with a statistically significant decrease in the risk of breast cancer ($P_{\text{trend}} = .008$); risk was reduced by 14% (95% confidence interval [CI]= 6% to 22%) for each additional birth. This association was the same for carriers of mutations in either BRCA1 or BRCA2 and was restricted to women older than 40 years. In BRCA2 mutation carriers, first childbirth at later ages was associated with an increased risk of breast cancer compared with first childbirth before age 20 years (20-24 years, HR = 2.33 [95% CI = 0.93 to 5.83], 25-29 years, HR = 2.68 [95% CI = 1.02 to 7.07], 30 or later, HR = 1.97 [95% CI = 0.67 to 5.81]), whereas in BRCA1 mutation carriers, first childbirth at age 30 or later was associated with a reduced risk compared with first childbirth before age 20 (HR = 0.58 [95% CI = 0.36 to 0.94]). Neither history of interrupted pregnancies nor history of breastfeeding was statistically significant associated with the risk of breast cancer. **Conclusions:** The number of full-term pregnancies are associated with a reduced risk of breast cancer among BRCA1/2 mutation carriers older than 40 years.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer worldwide with nearly 1,000,000 new cases diagnosed per year and the second leading cause of cancer deaths in women worldwide (1). Germline mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 confer high risks of breast and ovarian cancer (2, 3). In a combined analysis of 22 studies of breast cancer patients who were not selected on the basis of a family history of breast cancer,, the estimated risk of developing breast cancer was 65% by age 70 years among women who carried a deleterious mutation in the BRCA1 gene and 45% among those who carried a deleterious mutation in the BRCA2 gene (4). Up to 40% higher estimated risks of breast cancer have been found in studies of breast cancer patients with a strong family history of the disease (5, 6). The difference in these risk estimates suggests the existence of genetic or shared environmental factors within families that modify the risk of breast cancer (7).

BRCA1 and BRCA2 are tumor suppressor genes that are involved in multiple processes, including DNA damage repair and recombination, cell cycle control, transcription, and estrogen receptor- α activity (8, 9). In addition, Thompson et al. (10) reported that decreased levels of Brca1 protein increased the growth of tumor cells, whereas increased expression of the BRCA1 gene led to cell growth arrest and apoptosis. In vitro studies have also shown that BRCA1 gene expression was increased in proliferating cells undergoing differentiation especially during pregnancy and puberty. Control of cell proliferation stimulated by increased levels of estrogen during puberty and pregnancies may be compromised in BRCA1/BRCA2 heterozygote breast cells (9, 14). Therefore, these heterozygote breast cells may be more susceptible to genotoxic carcinogens than normal breast cells during the period from menarche to first childbirth when breast cells are undifferentiated (11–13). For all these reasons, the associations between the occurrence and

timing of reproductive events, like pregnancies or breastfeeding, and risk of breast cancer may differ in the general population and in BRCA1/2 mutation carriers.

Many studies (e.g. 15) have established that women who had their first full-term pregnancy at a young age before 25 years have a lower risk of breast cancer than nulliparous women or women who had their first full-term pregnancy when they were above 30 years; additional pregnancies are associated with even lower risks. Long-term breastfeeding is also associated with a decreased risk of breast cancer in the general population (16). Neither induced nor spontaneous abortion is associated with an increased risk of breast cancer (17). . The few studies that have examined associations between reproductive history and the risk of breast cancer among BRCA1/2 mutation carriers have produced inconsistent results. In some studies (19,21,23), the authors observed a decreased risk of breast cancer among nulliparous BRCA1/2 mutation carriers and an increased risk of breast cancer with increasing number of full-term pregnancies; in other studies (18,20,22), breast cancer risk was not associated with either the number of full-term pregnancies or young age at first full-term pregnancy. Only two studies have examined associations between breastfeeding history and the risk of breast cancer: one study found that breastfeeding was associated with a decreased risk among BRCA2 mutation carriers (21), whereas the other study found that breastfeeding was associated with a decreased risk of breast cancer among BRCA1 mutation carriers but not among BRCA2 mutation carriers (24). One study reported that miscarriages or abortions were not associated with an increased risk of early-onset breast cancer in BRCA1/2 mutation carriers (19).

To provide a better assessment of the risk of breast cancer to individual carriers of BRCA1 and BRCA2 mutations, we examined associations between reproductive history, including the number of pregnancies, age at first pregnancy, and history of breastfeeding and the risk of breast cancer in women who carried BRCA1 and BRCA2 gene mutations using

data obtained from the International BRCA1/2 Carrier Cohort Study (IBCCS), which includes most of the large population-based studies in Europe.

SUBJECTS AND METHODS

Study Group

The IBCCS was initiated in 1997 by the International Agency for Research on Cancer to prospectively estimate the risks of breast, ovarian, and other cancers in BRCA1/2 mutation carriers and to assess the lifestyle and genetic factors that may modify those risks. One of the aims of the IBCCS was to assess the role of reproductive factors as potential modifiers of cancer risks in BRCA1/2 mutation carriers. Details of the design and rationale of the IBCCS have been previously described (25). Any woman who was known to carry a presumed disease-predisposing mutation in the BRCA1 gene or the BRCA2 gene was eligible for enrollment in the IBCCS, including those who had been diagnosed with cancer (at any site), as well as those who were currently unaffected, if they were at least 18 years old, mentally capable of giving informed consent to study participation, and had been counseled about their mutation status. Subjects were ascertained from family cancer clinics, most of which required at least a 10–20% prior probability of carrying a mutation in BRCA1 or BRCA2 for performing mutation screening. The mutation screening strategy was similar across the family cancer clinics of the IBCCS: the youngest living affected (i.e., diagnosed with breast cancer) family member was tested first and, if a BRCA1/2 mutation was found, additional affected and unaffected family members were offered testing.

Our retrospective analyses were based on 1601 eligible women, 1187 (74.1%) of whom had BRCA1 mutations and 414 (25.9%) of whom had BRCA2 mutations, who were recruited into the IBCCS from January 1997 to December 2002. All of the women in our study were European, except for 88 subjects from Quebec, Canada. Approximately two-thirds (1064/1601) of subjects included in our study were participants in large ongoing

national studies of BRCA1/2 mutation carriers in the United Kingdom and Eire (the EMBRACE study), Netherlands (the GEO-HEBON study), and France (the GENEPSO study). The 1601 women were members of 764 families with one participant, 192 families with two participants; 67 families with three participants; 30 families with four participants; 11 families with five participants; three families with six participants; three families with seven participants; and four families which have eight, nine, 10, and 11 participants each, respectively .

A standardized questionnaire was administered to the study subjects either by mail, at an in-person interview at the time of genetic counseling, or through a telephone interview, depending on the study center. The questionnaire collected detailed information on pregnancy history. Subjects who indicated that they had had at least one pregnancy were asked to provide, for each pregnancy, the month and year when pregnancy started or was terminated, its duration, and its outcome (live birth, still birth, miscarriage, induced abortion), and the duration of breastfeeding, if applicable. The research protocol was approved by the relevant ethics committees and all participants provided written informed consent.

Statistical Methods

Factors associated with breast cancer risk were analyzed using a modified Cox proportional hazards regression model. We used a modified model instead of standard Cox proportional hazards regression modeling, which might have led to biased estimates of the hazard ratio because the women in this study were selected from high-risk families who qualified for genetic testing for breast cancer susceptibility. The likelihood to opt for genetic testing and being ascertained may be increased in women affected by breast cancer, leading to an over-sampling of affected women. To eliminate this potential bias, the analyses were performed using a weighted regression approach (26), in which case patients (affected women) and control subjects (unaffected women) were differentially weighted such that the observed breast cancer incidence rates in the study sample were consistent with the birth

cohort-specific breast cancer risk estimates for BRCA1 and BRCA2 mutation carriers that were reported by Antoniou et al. (4). In effect, the affected mutation carriers were underweighted (weights <1) and the unaffected mutation carriers were overweighted (weights > 1). The weights were applied to all person-years of each subject in the modified Cox model.

Subjects were censored at the date of diagnosis, for women who were affected by any cancer, or the date of interview, for unaffected women. Of the 879 women who had been diagnosed with breast cancer at the time of their interview, only 853 were classified as affected in this analysis because we excluded the 26 women who were diagnosed with breast cancer after being diagnosed with another cancer (most were previously diagnosed with ovarian cancer). The information on the histology of prevalent cases of breast cancer was not available and therefore the proportion of invasive versus in situ carcinoma is unknown, although a negligible number of BRCA1/2 carriers develops in situ carcinoma. The remaining 748 women who had not been diagnosed with breast cancer at the time of their interview were censored at: age at diagnosis of ovarian cancer (122 subjects); age at diagnosis of cancer other than ovarian cancer (16 subjects); age at which they underwent prophylactic bilateral mastectomy (31 subjects); or age at interview (579 subjects).

All analyses were performed using robust variance estimators which accounted for correlations in the risk factors between family members (27). Analyses were conducted for the entire cohort and separately for subjects with mutations in BRCA1 and BRCA2, as well as by attained age (40 years or younger versus older than 40 years. This 40 years cutpoint was chosen because, in the general population, the reduction in breast cancer risk associated with increasing number of births has been observed to become apparent after age 40 years.

Parity and menopausal status changed over time; therefore, they were analyzed as time-dependent covariates and therefore, accounted for any potential interaction with time.

Because the duration of an individual breast-feeding period was usually less than 1 year, the total duration of breast-feeding, which was calculated by summing up all breast-feeding periods, was considered as a fixed variable from the age of the woman when she first breast-fed until her age at censure. To avoid the potential bias due to breast cancer detected during a pregnancy which may cause a bias either towards or away from the null depending on the effect of pregnancy on the risk of breast cancer, pregnancies were only included if they occurred at least 1 year before the age at censure. Thus, we excluded 23 pregnancies, 15 among affected women and eight among unaffected women, all of which occurred after a full-term pregnancy. Menopausal status was defined by the subject's menstruation status 2 years before her age at diagnosis or censure. Women who had undergone hysterectomy without oophorectomy were classified as having an unknown menopausal status. All analyses were stratified by the year of birth (before 1940, 1940–1949, 1950–1959, 1960 or later) and country of residence group (group 1: Austria, Belgium, Germany, Holland, and Hungary; group 2: Iceland, Denmark, and Sweden; group 3: France, Spain, Italy, and Canada (Quebec); group 4: United Kingdom and Eire). In addition, because early oophorectomy may substantially modify the risk of breast cancer and thus be a potential confounder, all analyses were adjusted for oophorectomy (yes/no) as a time-dependent variable. Other potential confounders, such as oral contraceptive use, were examined and were not found to change the results. Eighteen women (16 affected, two unaffected) who had missing values for age at pregnancy were excluded from the analysis.

All statistical analyses were two-sided and were performed using the STATA statistical package (version 7; Stata Corporation, College Station TX).

RESULTS

Characteristics of the entire cohort and the distribution of reproductive variables are presented in Table 1. The characteristics of the women were similar across countries. The mean age (\pm standard deviation) of the entire cohort at interview was 46.7 years (± 12.0 years), ranging from 44 years (Austria) to 55 years (Iceland). The mean age at censor among affected women was 41.6 years (± 9.0 years), ranging from 39.3 years (The Netherlands) to 47.3 years (Iceland); the mean age at censor among unaffected women was 41.4 years (± 11.2 years), ranging from 38.6 years (Austria) to 44.5 years (Quebec). Among affected women, the mean time from their diagnosis of breast cancer to the interview was 8.6 years (± 7.4 years), ranging from 7.2 years (Spain) to 12.2 years (Germany).

The mean age at censor for the 748 women unaffected by breast cancer was similar to the mean age at diagnosis for the 853 women with breast cancer; however, the mean age at interview of the women with breast cancer was substantially older than that of the unaffected women. There was a total of 65,675 person-years of observation. The estimated risks of breast cancer associated with parity, age at pregnancy, and history of abortion from the weighted Cox regression analysis are summarized in Table 2, both for the entire cohort and for BRCA1 and BRCA2 mutation carriers. We also analyzed all of these variables according to attained age (40 years or younger versus older than 40 years) and present only the results of analyses by attained age that showed statistically significant evidence of heterogeneity. Overall, compared with nulliparous women, parous women had a slightly lower risk of breast cancer (HR = 0.85, 95% confidence interval [CI] = 0.66 to 1.11). Similar results were observed for all birth cohorts (data not shown). Among parous women, an increasing number of full-term pregnancies was associated with a statistically significant decrease in the risk of breast cancer ($P_{\text{trend}} = .008$). The reduction in risk was estimated to be 14% (95% CI = 6% to

22%) for each additional birth. This association was restricted to women older than 40 years (risk reduction per each additional birth =15%, 95% CI = 5% to 23%); among women who were 40 years or younger, the risk of breast cancer per additional birth increased by 10%, 95% CI = -10% to 34% (P for interaction =.029). In particular, compared with having one or two full-term pregnancies, having three or more full-term pregnancies was associated with reduced risk of breast cancer for women older than 40 years (HR = 0.72, 95% CI = 0.54 to 0.96) but not for women 40 years old or younger (HR = 1.21, 95% CI = 0.80 to 1.84). The reduction in risk associated with parity was similar in mutation carriers of either BRCA1 or BRCA2. We did not detect a transient increase in breast cancer risk either after the first full-term pregnancy or after the most recent pregnancy (data not shown).

Among parous women, age at first full-term pregnancy was not statistically significantly associated with breast cancer risk. However, there was a suggestion that the association between age at first full-term pregnancy and breast cancer risk differed between BRCA1 and BRCA2 mutation carriers ($P = .07$ for the interaction between mutant BRCA gene and age at first full-term pregnancy as continuous covariate). For example, among BRCA2 mutation carriers, there was some evidence that woman who had their first pregnancy when they were 20 years or older had a higher risk of breast cancer than women who had their first pregnancy when they were younger than 20 years. By contrast, among BRCA1 mutation carriers, women who had their first pregnancy when they were 20 years or older had a lower risk of breast cancer than women who had their first pregnancy when they were younger than 20 years (HR for those who experienced their first pregnancy at age 30 or later versus those who experienced their first pregnancy before age 20 = 0.58 [95% CI = 0.36 to 0.94]; $P_{\text{trend}} = .03$).

We found no association between having an interrupted pregnancy (due to miscarriage or an induced abortion) and the risk of breast cancer for women who carried a

mutation in either BRCA gene. There was also no association between the timing of an interrupted pregnancy with respect to the first full-term pregnancy and the risk of breast cancer (Table 2).

After adjusting for parity, we observed no association between ever having breastfed and breast cancer risk, either for the entire cohort or separately for BRCA1 or BRCA2 mutation carriers (Table 3). There was also no statistically significant association between duration of breastfeeding and breast cancer risk. Compared to never having breastfed, breastfeeding for more than 12 months was associated with a reduced risk for breast cancer in the entire cohort (HR = 0.89, 95% CI = 0.62 to 1.27) and the association was also not statistically significant in either BRCA1 or BRCA2 mutation carriers. Because whether and how long a woman breast feeds may vary by calendar year and by her country of residence, we performed the analyses according to birth cohort and country group as defined above and found that the risk estimates did not change.

For comparison, we also performed a standard (i.e., unweighted) Cox regression analysis of the data. The associations were generally in the same direction as those obtained in the weighted analysis but were biased towards the null. For example, in the unweighted analysis, the HRs associated with two, three, and four or more full-term pregnancies and nulliparity compared with one full-term pregnancy were 0.84 95% CI = 0.72 to 1.05, 0.76, 95% CI = 0.61 to 0.95, 0.68, 95% CI = 0.51 to 0.91 and 1.01 95% CI = 0.81 to 1.26 and in the weighted analysis, these HRs were 0.85, 95% CI = 0.65 to 1.13, 0.68, 95% CI = 0.49 to 0.95, 0.65, 95% CI = 0.42 to 1.00, 0.97, 95% CI = 0.70 to 1.33 .

To minimize any potential survival bias, we also performed analyses that were restricted to women who were diagnosed or censored during the 5 years before their interview, that is, including follow-up time accrued only in the last five years before interview . This cohort, which we refer to as the “pseudo-incident cohort”, yielded risk

estimates that were comparable to those obtained using the entire cohort except that the 95% confidence intervals were usually wider (e.g., HR associated with parity for the pseudo-incident cohort = 0.73 [95% CI = 0.48 to 1.12] versus HR for the entire cohort = 0.85 [95% CI = 0.66 to 1.11])

DISCUSSION

Our results indicate that the risk of breast cancer in parous BRCA1/2 mutation carriers is not statistically significantly different from that in nulliparous mutation carriers. However, in parous BRCA1/2 mutation carriers, the risk of breast cancer decreased by approximately 14% for each additional birth. This risk reduction, however, appeared to be restricted to women older than 40 years. The protective effect associated with number of full-term pregnancies appeared to be similar in BRCA1 and BRCA2 mutation carriers, and was roughly comparable to that seen for breast cancer in the general population ; in the largest dataset analyzed, the estimated risk reduction, was 7.0% (SE 1.0%) with each additional birth in women who had never breastfed (15) We found some evidence that the association between age at first full-term pregnancy and breast cancer risk differed in BRCA1 and BRCA2 mutation carriers. For BRCA2 mutation carriers, full-term pregnancy before the age of 20 years was associated with a lower risk of breast cancer than later age at first pregnancy, whereas in BRCA1 mutation carriers, later age at first pregnancy appeared to be associated with a lower risk of breast cancer. Neither interrupted pregnancies nor history of breastfeeding were associated with the risk of breast cancer in this cohort. However, considering that the estimated relative risk reduction associated with duration of breastfeeding in the general population is quite modest (4.3% for every 12 months of breastfeeding, according to the collaborative group on Hormonal Factors in Breast Cancer [15]), our data can not rule out a risk reduction of this magnitude.

Our study has several limitations. First, our results are based on retrospective information obtained from women who opted for BRCA mutation screening and genetic testing. And one assumption that underlies the method of weighting used in our analyses is that the absolute disease risks are well estimated and ascertainment is not dependent on the covariates of interest (26). This assumption would be violated if having children changed the likelihood of women to opt for genetic testing. This was indeed observed in two studies, including both affected and unaffected women, that the uptake of genetic testing was greater in women with children than in nulliparous women (28, 29). Unfortunately the magnitude of the potential bias when this assumption is violated has not been investigated. However, if ascertainment was associated with high parity, the difference in the number of children between affected and unaffected women would be reduced and weighting would lead to results that were biased toward the null rather than results that overestimated associations. Moreover, if parity was indeed associated with a reduced risk of breast cancer in BRCA1/2 mutation carriers, tested individuals with higher parity would, in effect, be susceptible to lower breast cancer risks than the breast cancer risks used to compute the weights. Consequently, the weights assigned to women with breast cancer would be too low thus resulting in estimates which are biased toward the null as shown by the simulations in Antoniou et al. (26). Bias could also arise if unaffected women are more likely to choose to undergo testing when they have children and affected women are more likely to opt for a test because of their diagnosis of breast cancer. We are unaware of any study that has assessed whether uptake of genetic testing in women differs according to her breast cancer affection status as well as the number of children she has borne and we cannot assess this potential bias using available IBCCS data. However, this possible bias will be explored further by using data from the GEO study being conducted in The Netherlands; this study is collecting detailed information from women who opted for genetic testing for BRCA genes and from

those who did not. Nevertheless, the influence of reproductive factors on genetic testing might differ by country and this possibility warrants further study in other populations as well.

Second, the difference in birth year between affected and unaffected women could be another source of bias in our study, particularly if the reproductive patterns in our study population have changed substantially across birth cohorts. For example, the unaffected women were born an average of 7 years later than the affected women. To correct for this potential bias, all of our analyses were performed stratified by the year of birth (in decades). The method used for weighting, which was cohort-specific, also contributed to correcting this potential bias. Moreover, we assessed this possible bias by analyzing the data by birth cohort and found similar HRs for childbearing and breastfeeding for all birth cohorts.

Another possible bias that might have influenced our results is survival bias resulting from the inclusion of affected women who survived long enough to participate in this study. Thus, some of the observed associations might, in part, be related to the breast cancer prognosis rather than to the risk of breast cancer. We therefore analyzed data from the pseudo-incident cohort to evaluate the effect of such a bias on our findings. We cannot totally exclude the possibility that a residual survival bias remained in the pseudo-incident cohort because some women with early-onset breast cancer who had a poor prognosis may not have still been alive 5 years later to participate in our study. However, the results based on the pseudo-incident cohort were not substantially different from those based on the entire cohort, suggesting that survival had negligible effect on our results.

In the general population, pregnancy is associated with a reduced risk of breast cancer. However, there is a transient increase in breast cancer risk after each birth, which is then followed by a reduced risk of breast cancer, so that the association between pregnancy and a reduced risk of breast cancer only becomes evident in women who are older than 40 or

50 years (30–32). The magnitude of the risk reduction associated with childbirth that we observed in our cohort of BRCA1/2 mutation carriers is consistent with that observed in the general population. However, we did not detect any transient increases in risk in our cohort. The mechanisms responsible for the long-term association between a full-term pregnancy and a reduced risk of breast cancer may differ between BRCA1/2 mutation carriers and the general population. Most previous studies of BRCA1/2 mutation carriers have not found statistically significant associations between childbearing and the risk of breast cancer (17, 19, 20). However, these studies were small and their estimated relative risks are, therefore, imprecise. Only one study has reported an association between parity and a reduced risk of breast cancer in BRCA1 mutation carriers (23). Our results are consistent with those of Jernström et al. (19), who also found that the risk of breast cancer by age 40 years in BRCA1/2 mutation carriers increased with the number of full-term pregnancies. However, in that case–control study, women who were diagnosed with breast cancer after age 40 years were also used as age-matched control subjects for case patients who were younger than 40 years at breast cancer diagnosis. Thus, Jernström et al. (19) might have overestimated the risk of breast cancer associated with childbearing by age 40 years if childbearing was associated with a reduced risk of breast cancer after age 40 years. More recently, the same group published results of a case–control study that was based on a larger sample of 1,260 matched sets and found that the risk of breast cancer increased with increasing parity, but only among BRCA2 mutation carriers who were 50 years or younger (33). In this analysis, again, breast cancer case patients were only included if they could be matched to a control subject. Thus, the survival bias might have been even more exaggerated by excluding as control subjects all women who had developed breast cancer at any time. It would be useful to evaluate how much the matching strategy as well as the familial clustering of mutation carriers in that study affected the results.

In the general population, younger age at first birth is associated with decreased risk of breast cancer (34). The association between high parity and a reduced risk of breast cancer has been found to be particularly strong among women who first gave birth before the age of 20 years (35). In our study, we observed a reduced risk of breast cancer among BRCA2 mutation carriers who had a full-term pregnancy before age 20. However, among BRCA1 mutation carriers, the risk of breast cancer was inversely related to the woman's age at first birth. Other studies of BRCA1 and BRCA2 mutation carriers that examined the effect of a woman's age at first birth found no decreased risk associated with a young age at first childbirth (20,21). One of those studies (20) found that mothers of BRCA1/2 mutation carriers who had their first full-term pregnancy after age 30 years had a lower risk of developing breast cancer than mothers of BRCA1/2 mutation carriers who had their first full-term pregnancy before age 25 years. These findings are compatible with our observations for BRCA1 mutation carriers (18). Although the difference in the pattern of risk between BRCA1 and BRCA2 mutation carriers that we observed might be due to chance, it might also reflect real differences in the natural history of breast cancer in BRCA1 and BRCA2 mutations carriers. In particular, BRCA1 mutations confer a much greater risk of breast cancer at very young ages than do BRCA2 mutations, and invariably predispose women who carry such mutations to estrogen receptor-negative tumors (36).

The BRCA1 gene is thought to play a key role in the normal proliferation and differentiation of cells in the mammary gland. For example, in mice BRCA1 expression is regulated during mammary gland development and increases during puberty and pregnancy, possibly to limit proliferation and promote differentiation (37). Recent studies in cell lines and in rats have shown that estrogens may increase expression of BRCA1, which decreases the activity of estrogen receptor- α -mediated pathways, thereby suppressing cell proliferation (9, 14, 38). In some experimental animal models, susceptibility to mammary cancer is

strongly related to the proliferation of the mammary epithelial cells and inversely related to the degree of differentiation (11). Pregnancy furthers the differentiation of the terminal end buds and induces dramatic changes in the parenchyma-stroma ratio of breast tissue, thereby conferring protection against the development of breast cancer (11). The lobular architecture of the breast tissue in parous women who had a family history of breast cancer was found to resemble that of nulliparous women without a family history rather than that of parous women without a family history (39). Thus, it was postulated that the breast tissue from women with hereditary breast cancer suffers from a disturbance of cell differentiation following pregnancy and altered interactions between the epithelium and the stroma (39). Nevertheless, a higher proportion of more differentiated lobular structures in the parous than nulliparous women was also observed in women from hereditary breast cancer families (39). These observations support the hypothesis that pregnancy is associated with a reduced risk for breast cancer in BRCA1/2 mutation carriers, but also raise the possibility that the extent and pattern of this protective effect may be different from that observed in the general population.

In conclusion, our data provide evidence that multiple full-term pregnancies are associated with a moderate reduction in the risk of breast cancer in BRCA1 and BRCA2 mutation carriers, which is only evident in women older than 40 years. This decrease in breast cancer risk appears to be consistent with that found in the general population. Further studies are needed to understand the mechanisms underlying the observed long term protective effect of full-term pregnancies on breast cancer risk. Nevertheless, the decrease in risk of breast cancer associated with multiple pregnancies might be used to revise the risk estimates given to BRCA1/2 mutation carriers. The association of age at first full-term pregnancy with breast cancer risk, however, were less consistent with that seen in the general

population and might differ by gene. These findings may reflect differences in the pathogenesis of cancers associated with the two genes and warrants further investigation.

NOTES

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Table 1. Characteristics of the cohort study of BRCA1/2 mutation carriers*

Characteristic	Total cohort (N=1601)		Women with breast cancer (N=853)		Unaffected women (N=748)	
			BRCA1 mutation carriers (N=602)	BRCA2 mutation carriers (N=251)	BRCA1 mutation carriers (N=585)	BRCA2 mutation carriers (N=163)
No. person-years of follow-up	65675	602	251	47342	17480	
Mean age at interview, y (SD)	46.7 (12.0)	49.5 (10.7)	51.4 (10.8)	42.5 (12.6)	44.0 (11.1)	
Mean age at diagnosis/censure, y (SD)	41.5 (10.1)	40.8 (9.0)	43.5 (8.8)	40.9 (11.4)	43.1 (10.5)	
Year of birth, No. (%)						
Before 1940	223 (13.9)	97 (16.1)	54 (21.5)	56 (9.6)	16 (9.8)	
1940–1949	356 (22.2)	161 (26.7)	71 (28.3)	92 (15.7)	32 (19.6)	
1950–1959	494 (30.9)	214 (35.6)	82 (32.7)	152 (26.0)	46 (28.2)	
1960 or later	528 (33.0)	130 (21.6)	44 (17.5)	285 (48.7)	69 (42.3)	
Country group [†] , No. (%)						
Group 1	358 (22.4)	148 (24.6)	31 (12.4)	153 (26.2)	26 (15.9)	
Group 2	171 (10.7)	45 (7.5)	36 (14.3)	76 (13.0)	14 (8.6)	
Group 3	530 (33.1)	213 (35.4)	86 (34.3)	174 (29.7)	57 (35.0)	
Group 4	542 (33.9)	196 (32.6)	98 (39.0)	182 (31.1)	66 (40.5)	
Menopausal status at censure, No. (%)						
Premenopausal	1228 (76.7)	469 (77.9)	196 (78.1)	444 (75.9)	119 (73.0)	
Postmenopausal						
Oophorectomy	55 (3.4)	13 (2.1)	4 (1.6)	29 (5.0)	9 (5.5)	
No oophorectomy	181 (11.3)	60 (10.0)	33 (13.1)	62 (10.6)	26 (16.0)	
Unknown	137 (8.6)	60 (10.0)	18 (7.2)	50 (8.5)	9 (5.5)	
Number of full-term pregnancies [‡] , No. (%)						
0	313 (19.6)	107 (17.8)	43 (17.1)	135 (23.1)	28 (17.2)	
1	247 (15.4)	113 (18.8)	29 (11.6)	81 (13.9)	24 (14.7)	
2	610 (38.1)	228 (37.9)	95 (37.8)	226 (38.6)	61 (37.4)	
3	281 (17.6)	105 (17.4)	43 (17.1)	98 (16.7)	35 (21.5)	

Characteristic	Total cohort (N=1601)		Women with breast cancer (N=853)		Unaffected women (N=748)					
			BRCA1 mutation carriers (N=602)	BRCA2 mutation carriers (N=251)	BRCA1 mutation carriers (N=585)	BRCA2 mutation carriers (N=163)				
≥4	132	(8.2)	48	(8.0)	26	(10.4)	44	(7.5)	14	(8.6)
Unknown	18	(1.1)	1	(0.2)	15	(6.0)	1	(0.2)	1	(0.6)
Age at first birth ^{†‡§} , No. (%)										
<20 years	149	(11.7)	65	(13.2)	13	(6.7)	53	(11.8)	18	(13.4)
20–24 years	508	(40.0)	216	(43.7)	74	(38.3)	176	(39.2)	42	(31.3)
25–29 years	441	(34.7)	159	(32.2)	80	(41.5)	153	(34.1)	49	(36.6)
≥30 years	172	(13.5)	54	(10.9)	26	(13.5)	67	(14.9)	25	(18.7)
Total time of breastfeeding ^{†§} , No. (%)										
0 months	352	(27.7)	139	(28.1)	58	(30.0)	122	(27.2)	33	(24.6)
1–5 months	365	(28.7)	161	(32.6)	41	(21.2)	129	(28.7)	34	(25.4)
6–12 months	276	(21.7)	107	(21.7)	43	(22.3)	99	(22.1)	27	(20.2)
13–24 months	148	(11.7)	49	(9.9)	21	(10.9)	60	(13.4)	18	(13.4)
>24 months	54	(4.3)	19	(3.9)	9	(4.7)	20	(4.4)	6	(4.5)
Unknown	75	(5.9)	19	(3.8)	21	(10.9)	19	(4.2)	16	(11.9)

*SD = standard deviation.

†Group 1: Austria, Belgium, Germany, Holland, and Hungary; group 2: Iceland, Denmark, and Sweden; group 3: France, Spain, Italy, and Canada (Quebec); group 4: United Kingdom and Eire.

‡At censure.

§Among parous women.

Table 2. Risk of breast cancer associated with parity, age at pregnancy, and abortion history*

Reproductive factors	Entire cohort			BRCA1 mutation carriers			BRCA2 mutation carriers		
	No. of person-years	No. of breast cancer cases	HR (95% CI)	No. of person-years	No. of breast cancer cases	HR (95% CI)	No. of person-years	No. of breast cancer cases	HR (95% CI)
Parity[†]									
Nulliparous	42,135	150	1.00 (referent)	31,167	107	1.00 (referent)	10,968	43	1.00 (referent)
Parous	22,737	687	0.85 (0.66 to 1.11)	16,702	494	0.86 (0.64 to 1.15)	6,035	193	0.79 (0.46 to 1.37)
No. of full-term pregnancies[†]									
1	6,235	142	1.00 (referent)	4,701	113	1.00 (referent)	1,534	29	1.00 (referent)
2	9,633	323	0.85 (0.65 to 1.13)	7,186	228	0.79 (0.59 to 1.05)	2,447	95	1.18 (0.62 to 2.25)
3	4,336	148	0.68 (0.49 to 0.95)	3,140	105	0.71 (0.50 to 0.99)	1,196	43	0.69 (0.30 to 1.58)
≥4	2,533	74	0.65 (0.42 to 1.00)	1,675	48	0.71 (0.45 to 1.10)	858	26	0.60 (0.22 to 1.60)
Nulliparous	42,135	150	0.97 (0.70 to 1.33)	31,167	107	0.94 (0.66 to 1.33)	10,968	43	1.20 (0.58 to 2.48)
No. of full-term pregnancies by attained age[†]									
≤40 years									
1–2	4,243	232	1.00 (referent)	3,424	183	1.00 (referent)	819	49	1.00 (referent)
≥3	765	71	1.21 (0.80 to 1.84)	609	55	1.15 (0.73 to 1.82)	156	16	1.62 (0.77 to 3.42)
Nulliparous	20,286	105	1.14 (0.81 to 1.60)	16,13	83	1.08 (0.76 to 1.55)	4,155	22	1.06 (0.48 to 2.37)
>40 years									
1–2	11,625	233	1.00 (referent)	8,463	158	1.00 (referent)	3,162	75	1.00 (referent)
≥3	6,104	151	0.72 (0.54 to 0.96)	4,206	98	0.83 (0.60 to 1.14)	1,898	53	0.47 (0.23 to 0.95)
Nulliparous	21,849	45	1.11 (0.71 to 1.73)	15,036	24	1.11 (0.67 to 1.86)	6,813	21	1.24 (0.51 to 2.99)
Age at first full-term pregnancy[†]									
<20 years	3,688	78	1.00 (referent)	2,801	65	1.00 (referent)	887	13	1.00 (referent)
20–24 years	10,688	290	1.01 (0.70 to 1.45)	8,019	216	0.84 (0.58 to 1.22)	2,669	74	2.33 (0.93 to 5.83)
25–29 years	6,602	239	0.92 (0.63 to 1.34)	4,646	159	0.77 (0.53 to 1.13)	1,956	80	2.68 (1.02 to 7.07)
≥30 years	1,759	80	0.71 (0.45 to 1.11)	1,236	54	0.58 (0.36 to 0.94)	523	26	1.97 (0.67 to 5.81)
Nulliparous	42,135	150	0.72 (0.44 to 1.16)	31,167	107	0.66 (0.40 to 1.09)	10,968	43	1.97 (0.54 to 7.23)

Reproductive factors	Entire cohort			BRCA1 mutation carriers			BRCA2 mutation carriers		
	No. of person-years	No. of breast cancer cases	HR (95% CI)	No. of person-years	No. of breast cancer cases	HR (95% CI)	No. of person-years	No. of breast cancer cases	HR (95% CI)
Abortion history[†]									
No full-term pregnancy or abortion	10,158	127	1.00 (referent)	7,505	88	1.00 (referent)	2,653	39	1.00 (referent)
Full-term pregnancy, no abortion	47,976	487	0.88 (0.60 to 1.27)	34,694	331	0.83 (0.55 to 1.26)	13,282	156	0.81 (0.36 to 1.81)
Induced abortion only	2,741	84	0.91 (0.57 to 1.45)	2,276	73	0.92 (0.56 to 1.51)	465	11	0.34 (0.11 to 1.08)
Miscarriage only	4,255	133	0.82 (0.52 to 1.29)	3,048	95	0.84 (0.51 to 1.39)	1,207	38	0.56 (0.21 to 1.48)
Induced abortion and miscarriage	447	21	1.21 (0.61 to 2.41)	323	14	1.01 (0.47 to 2.13)	124	7	1.52 (0.29 to 7.80)
Abortion relative to first full-term pregnancy[‡]									
No abortion	54,166	561	1.00 (referent)	40,746	403	1.00 (referent)	13,420	158	1.00 (referent)
Before first full-term pregnancy or no full-term pregnancy	3,804	116	0.90 (0.66 to 1.22)	2,840	86	0.99 (0.72 to 1.38)	964	30	0.54 (0.26 to 1.15)
After first full-term pregnancy	3,662	122	0.96 (0.72 to 1.27)	2,830	96	1.02 (0.75 to 1.38)	832	26	0.64 (0.32 to 1.28)

*Number of person-years of observation and number of breast cancer cases occurring in the specified cohort are presented. Estimated hazard ratios are stratified by birth cohort and country group. HR = hazard ratio; CI = confidence interval.

[†]Adjusted for oophorectomy.

[‡]Adjusted for oophorectomy and number of full-term pregnancies

Table 3. Risk of breast cancer associated with breastfeeding*

Variables	Entire cohort			BRCA1 mutation carriers			BRCA2 mutation carriers		
	No. of person-years	No. of breast cancer cases	HR (95% CI)	No. of person-years	No. of breast cancer cases	HR (95% CI)	No. of person-years	No. of breast cancer cases	HR (95% CI)
Breastfeeding history[†]									
Never	6,843	197	1.00 (referent)	5,014	139	1.00 (referent)	1,829	58	1.00 (referent)
Ever	14,340	450	1.04 (0.81 to 1.34)	11,007	336	1.07 (0.81 to 1.40)	3,333	114	0.79 (0.44 to 1.39)
Nulliparous	42,135	150	0.77 (0.52 to 1.16)	31,167	107	0.87 (0.56 to 1.36)	10,968	43	0.60 (0.24 to 1.53)
Duration of breastfeeding[†] (fixed covariate)									
0 month	6,843	197	1.00 (referent)	5,014	139	1.00 (referent)	1,829	58	1.00 (referent)
1–5 months	6,039	202	1.10 (0.82 to 1.47)	4,697	161	1.16 (0.85 to 1.59)	1,342	41	0.66 (0.33 to 1.31)
6–12 months	4,430	150	1.05 (0.76 to 1.46)	3,402	107	1.03 (0.72 to 1.47)	1,028	43	1.01 (0.49 to 2.06)
13–24 months	2,778	70	0.83 (0.56 to 1.23)	2,109	49	0.85 (0.55 to 1.33)	669	21	0.58 (0.25 to 1.33)
>24 months	1,093	28	1.08 (0.62 to 1.89)	799	19	1.01 (0.57 to 1.79)	294	9	1.21 (0.32 to 4.54)
Nulliparous	42,135	150	0.80 (0.53 to 1.21)	31,167	107	0.91 (0.58 to 1.44)	10,968	43	0.61 (0.24 to 1.57)
Age at 1st breastfeeding and duration[†]									
0 months (all ages)	6,843	197	1.00 (referent)	5,014	139	1.00 (referent)	1,829	58	1.00 (referent)
<25 years									
≤12 months	6,214	163	1.12 (0.82 to 1.53)	5,053	134	1.13 (0.82 to 1.57)	1,161	29	0.69 (0.32 to 1.50)
>12 months	2,241	52	1.15 (0.71 to 1.85)	1,777	43	1.30 (0.78 to 2.16)	464	9	0.49 (0.15 to 1.65)
≥25 years									
≤12 months	4,255	189	1.05 (0.77 to 1.42)	3,046	134	1.09 (0.79 to 1.51)	1,209	55	0.86 (0.43 to 1.73)
>12 months	1,630	46	0.70 (0.45 to 1.10)	1,131	25	0.64 (0.39 to 1.05)	499	21	0.97 (0.38 to 2.47)
Nulliparous	42,135	150	0.77 (0.51 to 1.18)	31,167	107	0.87 (0.55 to 1.37)	10,968	43	0.69 (0.27 to 1.79)

*Number of person-years of observation and number of breast cancer cases occurring in the specified cohort are presented. Estimated hazard ratios stratified by birth cohort and country group.

[†]Adjusted for oophorectomy and number of children (continuous variable).