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Effect of pregnancy as a risk factor for breast cancer in *BRCA1*/*BRCA2* mutation carriers

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Early age at first birth and multiparity have been associated with a decrease in the risk of breast cancer in women in the general population. We examined whether this relationship is also present in women at high risk of breast cancer due to the presence of a mutation in either of the 2 breast cancer susceptibility genes, *BRCA1* or *BRCA2*. We performed a matched case-control study of 1,260 pairs of women with known *BRCA1* or *BRCA2* mutations, recruited from North America, Europe and Israel. Women who had been diagnosed with breast cancer were matched with unaffected control subjects for year of birth, country of residence, and mutation (*BRCA1* or *BRCA2*). Study subjects completed a questionnaire detailing their reproductive histories. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived by conditional logistic regression. Among *BRCA1* carriers, parity *per se* was not associated with the risk of breast cancer (OR for parous *vs.* nulliparous = 0.94; 95% CI = 0.75–1.19; $p = 0.62$). However, women with a *BRCA1* mutation and 4 or more children had a 38% decrease in breast cancer risk compared to nulliparous women (OR = 0.62; 95% CI = 0.41–0.94). In contrast, among *BRCA2* carriers, increasing parity was associated with an increased risk of breast cancer; women with 2 or more children were at approximately 1.5 times the risk of breast cancer as nulliparous women (OR = 1.53; 95% CI = 1.01–2.32; $p = 0.05$). Among women with *BRCA2* mutations and who were younger than age 50, the (adjusted) risk of breast cancer increased by 17% with each additional birth (OR = 1.17; 95% CI = 1.01–1.36; $p = 0.03$). There was no significant increase in the risk of breast cancer among *BRCA2* carriers older than 50 (OR for each additional birth = 0.97; 95% CI = 0.58–1.53; $p = 0.92$). In the 2-year period following a birth, the risk of breast cancer in a *BRCA2* carrier was increased by 70% compared to nulliparous controls (OR = 1.70; 95% CI = 0.97–3.0). There was a much smaller increase in breast cancer risk among *BRCA2* carriers whose last birth was 5 or more years in the past (OR = 1.24; 95% CI = 0.79–1.95). A modest reduction in risk of breast cancer was observed among *BRCA1* carriers with 4 or more births. Among *BRCA2* carriers, increasing parity was associated with a significant increase in the risk of breast cancer before age 50 and this increase was greatest in the 2-year period following a pregnancy.

Key words: parity; breast cancer; *BRCA* mutation

The lifetime risk of breast cancer among carriers of mutations in *BRCA1* or *BRCA2* is approximately 80%,[1,2] but individual risks may vary due to the effect of modifying factors.[3] Reproductive factors have long been known to be important in the risk of breast cancer in the general population.[4] In an earlier study, we reported that increasing parity was associated with an increased risk of early-onset (< 40 year of age) breast cancer in both *BRCA1* and *BRCA2* carriers.[5] However, the size of this study was small (189 matched pairs with *BRCA1* mutations and 47 matched pairs with *BRCA2* mutations) and the confidence limits were

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TABLE I – CHARACTERISTICS OF CASE AND CONTROLS

	Cases (n = 1,260)	Controls (n = 1,260)	p-value
Date of birth, mean (SD)	1,953.9 (10.0)	1,954.4 (9.9)	0.19
Current age, mean (SD)	45.9 (9.5)	45.4 (9.9)	0.22
Mutation, n (%)			
BRCA1	943 (74.1)	943 (74.1)	
BRCA2	326 (25.9)	326 (25.9)	
Country of residence, n (%)			
United States	553 (43.9)	553 (43.9)	
French-Canadian	97 (7.7)	97 (7.7)	
Other Canada	264 (21.0)	264 (21.0)	
Poland	158 (12.5)	158 (12.5)	
Israel	70 (5.6)	70 (5.6)	
Norway	35 (2.8)	35 (2.8)	
Sweden	8 (0.6)	8 (0.6)	
Italy	23 (1.8)	23 (1.8)	
France	2 (0.2)	2 (0.2)	
The Netherlands	21 (1.7)	21 (1.7)	
Austria	22 (1.8)	22 (1.8)	
United Kingdom	7 (0.6)	7 (0.6)	
Age at menarche, years (SD)	12.7 (1.5)	12.9 (1.5)	0.001
Oral contraceptive, ever use	885 (70.2)	910 (72.2)	0.27
Nulliparous, n (%)	287 (22.8)	294 (23.3)	0.74
Mean parity (SD)	1.75 (1.4)	1.80 (1.3)	0.40
Age at first birth	25.3 (4.7)	24.9 (4.6)	0.07
Age at last birth	29.4 (4.8)	29.3 (4.7)	0.44

wide. Since the publication of this original report, our study group has continued to accrue information on women with *BRCA1* and *BRCA2* mutations and we have reevaluated this association using a much larger sample of subjects.

Material and methods

Study population

Eligible women were selected from a registry of individuals assessed for genetic risk in 1 of 55 genetic counseling centers in North America, Europe, or Israel. Study subjects were women who attended a genetics clinic for the purpose of risk assessment and genetic counseling. All patients received their genetics test result (with the exception of those at the University of Utah, where patients were enrolled in a research study but did not receive their genetic test result). In most cases, the patient completed a questionnaire dealing with reproductive histories and cancer histories during one of the counseling sessions, but in some cases the questionnaire was mailed or was administered over the phone. Information was obtained on 6,133 carriers with deleterious mutations in *BRCA1* (n = 4,612) or in *BRCA2* (n = 1,521). The ethics committee or institutional review board at all participating centers approved this study and all women provided written informed consent. For the majority of cases, testing was initially offered to individuals with a diagnosis of breast or ovarian cancer. If a deleterious mutation was found, testing was offered to other at-risk family members. Mutations were initially identified using a variety of techniques, but all variant nucleotide sequences were confirmed with direct sequencing of DNA. The majority of women included in this study had nonsense mutations, deletions, insertions, or small frameshift mutations; these are known to confer an increased risk of breast cancer. Patients with variants of uncertain significance were not included in the study.

There were 2,959 women who had been diagnosed with breast cancer. Women were excluded if they had a diagnosis of ovarian cancer (n = 336) or if they had a bilateral oophorectomy prior to diagnosis (n = 182). Information about reproductive history or preventive surgery was missing for 368 subjects. There was a total of 2,073 eligible mutation carriers with breast cancer (cases). For each case, we attempted to identify a single eligible matched control that had not developed breast cancer. Controls were matched for year of birth (within 1 year of case), country of residence and mutation status (*BRCA1* or *BRCA2*). Canadian controls were also matched for ethnicity (French-Canadian and other). Controls were ineligible to be matched to a case if they had ovarian cancer or had a prophylactic mastectomy or oophorectomy prior to the date of diagnosis in the case. We were able to identify 1,260 matched pairs (934 *BRCA1* case-control pairs and 326 *BRCA2* case-control pairs).

Information about reproductive histories was recorded in questionnaires that were distributed to the study subject at the time of genetic testing or thereafter. On average, the questionnaire was completed 7.9 years after the diagnosis of breast cancer. The years of each pregnancy and the year of cancer diagnosis were recorded. If the year of pregnancy and the year of diagnosis were the same (120 women), then we could not determine the sequence of pregnancy and breast cancer and the pregnancy was not recorded. Pregnancy was defined as a pregnancy resulting in either a live birth or a stillborn child. For the control exposure, only pregnancies that occurred prior to the age of diagnosis in the matched cases were considered (if they occurred in the same year they were not considered).

Data analysis

Pregnancy histories of the cases were compared with those of the control subjects. McNemar's test was used to assess the statistical significance of these univariate comparisons. A paired t-test was used to compare continuous variables (such as age of menarche and parity) in a matched analysis. For parous cases and controls, this also included age at first birth and age at last birth. Conditional logistic regression was performed to estimate adjusted odds ratios using matched analyses. All statistical analyses were done using SAS 8.2 (SAS Institute, Cary, NC).

Results

Cases and controls were similar with respect to demographic and reproductive factors (Table I). There were no significant differences with respect to year of birth, country of residence, parity, or previous oral contraceptive use. The median age at interview of the case subjects was 45.9 years (range, 18.9–86.7 years) and of controls was 45.4 years (range, 23.4–84.7 years). The majority of the cases came from the United States and Canada, followed by Poland, Israel and Norway.

The effect of parity on breast cancer risk was examined. Compared to nulliparous women, parous *BRCA1* carriers had a similar

TABLE II – EFFECT OF PARITY ON BREAST CANCER RISK

Parity	BRCA1 (n = 934) OR (95% CI)	p-value	BRCA2 (n = 326) OR (95% CI)	p-value
Nulliparous	1		1	
Ever	0.94 (0.5–1.19)	0.62	1.37 (0.93–2.03)	0.12
Nulliparous	1		1	
1	0.92 (0.68–1.25)	0.60	1.03 (0.61–1.73)	0.91
2	1.03 (0.79–1.33)	0.84	1.48 (0.94–2.32)	0.09
3	0.89 (0.65–1.22)	0.47	1.68 (0.99–2.86)	0.05
4+	0.62 (0.41–0.94)	0.02	1.47 (0.77–2.80)	0.24
Risk per birth	0.94 (0.86–1.02)	0.62	1.15 (1.00–1.33)	0.05
p-value for trend	0.12		0.050	

TABLE III – EFFECT OF PARITY ON BREAST CANCER RISK BY AGE OF DIAGNOSIS

Age group (BRCA1 pairs/BRCA2 pairs)	BRCA1 (n = 934) OR (95% CI)	p-value	BRCA2 (n = 326) OR (95% CI)	p-value
< 40 (585/157)	0.91 (0.82–1.02)	0.10	1.19 (0.97–1.45)	0.10
40–44 (189/78)	1.07 (0.89–1.28)	0.47	1.17 (0.88–1.56)	0.29
45–49 (110/56)	0.88 (0.69–1.12)	0.29	1.10 (0.80–1.53)	0.55
50+ (50/35)	0.79 (0.51–1.22)	0.29	0.97 (0.58–1.53)	0.92
< 50 (884/291)	0.94 (0.86–1.03)	0.16	1.17 (1.01–1.36)	0.03

Odds ratios represent the increase in risk of breast cancer associated with each pregnancy.

TABLE IV – ODDS RATIOS FOR BREAST CANCER ACCORDING TO TIME SINCE LAST PREGNANCY

	BRCA1 (n = 934) OR (95% CI)	p	BRCA2 (n = 326) OR (95% CI)	p
Nulliparous	1		1	
1–2 years	0.72 (0.53–0.99)	0.04	1.70 (0.97–2.99)	0.07
3–5 years	0.94 (0.68–1.29)	0.68	1.38 (0.79–2.39)	0.25
6+ years	1.10 (0.84–1.43)	0.50	1.24 (0.79–1.95)	0.36

risk of breast cancer (OR = 0.94; 95% CI = 0.75–1.19; p = 0.62). However, parity above 3 appeared to be protective (OR = 0.62; p = 0.02; Table II). Parous *BRCA2* carriers had a nonsignificantly elevated risk of breast cancer compared to nulliparous women (OR = 1.37; 95% CI = 0.93–2.03; p = 0.12). Among *BRCA2* carriers, the risk of breast cancer increased by 15% with each additional birth (p for trend = 0.05).

The observed effect of parity on breast cancer risk in *BRCA2* carriers appeared to be restricted to women who were diagnosed before age 50 (Table III). Among women below age 50, and with a *BRCA2* mutation, the odds ratio for breast cancer with each additional birth was 1.17 (95% CI = 1.01–1.36; p = 0.03) and for women diagnosed after age 50 was 0.97 (95% CI = 0.58–1.53).

To examine the possibility that there is a transient increase in the incidence of breast cancer following pregnancy, we compared cases and controls for time elapsed from last pregnancy (Table IV). Compared to nulliparous women with *BRCA2* mutations, those with a pregnancy in the last 2 years had a moderate increase in breast cancer risk (OR = 1.70; 95% CI = 0.97–2.99). For women whose last pregnancy was 2–5 years in the past, this risk was modestly increased (OR = 1.38; 95% CI = 0.79–2.39). There was a smaller increase in risk for *BRCA2* carriers whose last pregnancy was 5 or more years in the past (OR = 1.24; 95% CI = 0.79–1.95). Among BRC1 carriers, there was a modest reduction in breast cancer risk in the 2 years following a pregnancy (OR = 0.72; p = 0.04).

Discussion

Several of the risk factors that are believed to contribute to the development of breast cancer are thought to be related to the hormonal milieu to which the breast is exposed. Age at first full-term pregnancy is an accepted risk factor; early pregnancies and multiparity are protective, whereas a first full-term pregnancy occurring after the age of 30 is believed to increase risk.[4,6,7] Due in part to the relatively younger age at diagnosis of breast cancer in BRCA carriers, it has been hypothesized that pregnancy might increase the risk of hereditary breast cancer because of the mitogenic influence of increased levels of estrogen and progesterone upon mammary tissue.

Pregnancy-associated breast cancer (defined as breast cancer diagnosed during pregnancy or within 1 year of giving birth) is estimated to occur in 10–39 women per 100,000 live births.[8] Recent studies have shown a transient increase in breast cancer risk immediately after pregnancy.[8–10] A study of 265 women with pregnancy-associated breast cancer in Sweden reported 12 carriers of a *BRCA1* mutation and 3 carriers of a *BRCA2* mutation.[11] There was a significant excess of pregnancy-associated breast cancers in women with germline *BRCA1* mutations (OR = 3.9; 95% CI = 1.4–10.8) and an nonsignificant increase in women with *BRCA2* mutations (OR = 1.9; 95% CI = 0.5–7.0). We observed that the risk of breast cancer was increased by approximately 70% in the 2-year period following pregnancy in *BRCA2* carriers, but there was no comparable increase in risk among women with *BRCA1* mutations.

Though exposure to estrogen has been associated with an increased risk of breast cancer, the differential risk of breast cancer seen in *BRCA1* and *BRCA2* mutation carriers associated with pregnancy suggests that responses to hormonal influences may be distinct in the 2 subgroups.

In our previous study of 236 cases and matched controls, we reported that parous carriers of a mutation in either gene were significantly more likely to develop breast cancer by age 40 than nulliparous carriers.[5] In this much larger current sample of 1,260 matched sets, the increase in the risk of breast cancer with increasing parity was restricted to *BRCA2* carriers. However, the risk increase was modest and of borderline significance. We have recently shown that breast-feeding is protective against breast cancer in *BRCA1* carriers, but a similar reduction in risk was not seen for *BRCA2* carriers.[12] These data present important implications in the risk assessment and clinical management of this group of patients. Women with *BRCA2* mutations may benefit from more intensive surveillance in the 5-year period following childbirth or may wish to consider prophylactic breast surgery once childbearing is complete.

References

1. Ford D, Easton DF, Stratton M, Narod SA, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, *et al*. Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families: the Breast Cancer Linkage Consortium. Am J Hum Genet 1998;62:676–89.
2. Antoniou A, Pharoah PD, Narod SA, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, *et al*. Average risks of breast and ovarian cancer associated with *BRCA1* or *BRCA2* mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117–30.
3. Narod SA. Modifiers of risk of hereditary breast and ovarian cancer. Nat Rev Cancer 2002;2:113–23.
4. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG. "Hormonal" risk factors, "breast tissue age" and the age-incidence of breast cancer. Nature 1983;303:767–70.
5. Jernstrom H, Lerman C, Ghadirian P, Lynch HT, Weber B, Garber J, Daly M, Olopade OI, Foulkes WD, Warner E, Brunet JS, Narod SA. Pregnancy and risk of early breast cancer in carriers of *BRCA1* and *BRCA2*. Lancet 1999;354:1846–50.
6. Ewertz M, Duffy SW, Adami HO, Kvale G, Lund E, Meirik O, Mellemgaard A, Soini I, Tulinius H. Age at first birth, parity and risk of breast cancer: a meta-analysis of 8 studies from the Nordic countries. Int J Cancer 1990;46:597–603.
7. Chie WC, Hsieh C, Newcomb PA, Longnecker MP, Mittendorf R, Greenberg ER, Clapp RW, Burke KP, Titus-Ernstoff L, Trentham-Dietz A, MacMahon B. Age at any full-term pregnancy and breast cancer risk. Am J Epidemiol 2000;51:715–22.
8. Gemignani ML, Petrek JA. Pregnancy-associated breast cancer: diagnosis and treatment. Breast J 2000;6:68–73.
9. Liu Q, Wuu J, Lambe M, Hsieh SF, Ekbom A, Hsieh CC. Transient increase in breast cancer risk after giving birth: postpartum period with the highest risk (Sweden). Cancer Causes Control 2002;13:299–305.
10. Leon DA, Carpenter LM, Broeders MJ, Gunnarskog J, Murphy MF. Breast cancer in Swedish women before age 50: evidence of a dual effect of completed pregnancy. Cancer Causes Control 1995;4:283–91.
11. Johannsson O, Loman N, Borg A, Olsson H. Pregnancy-associated breast cancer in *BRCA1* and *BRCA2* germline mutation carriers. Lancet 1998;352:1359–60.
12. Jernstrom H, Lubinski J, Lynch HT, Ghadirian P, Neuhausen S, Isaacs C, Weber BL, Horsman D, Rosen B, Foulkes WD, Friedman E, Gershoni-Baruch R, *et al*. Breast-feeding and the risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers. J Natl Cancer Inst 2004;96:1094–8.