Family History of Cancer and Cancer Risks in Women with BRCA1 or BRCA2 Mutations

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Women who carry a deleterious mutation in BRCA1 or BRCA2 have high lifetime risks of breast and ovarian cancers. However, the influence of a family history of these cancers on these risks in women with BRCA mutations is unclear. We calculated cancer incidence rates for a multinational cohort comprising 3011 women with BRCA1 or BRCA2 mutations who were followed up for a mean of 3.9 years, during which time 243 incident breast or ovarian cancers were recorded. The 10-year cumulative risks of breast cancer were 18.1% (95% confidence interval [CI] = 13.3% to 22.8%) for women with a BRCA1 mutation and 15.2% (95% CI = 9.1% to 21.2%) for women with a BRCA2 mutation. Among women with a BRCA1 mutation, the risk of breast cancer increased by 1.2-fold for each first-degree relative with breast cancer before age 50 years (hazard ratio [HR] = 1.21; 95% confidence interval [CI] = 0.94 to 1.57) and the risk of ovarian cancer increased by 1.6 fold for each first- or second-degree relative with ovarian cancer (HR = 1.61; 95% CI = 1.21 to 2.14). Among women with a BRCA2 mutation, the risk of breast cancer increased by 1.7-fold for each first-degree relative younger than 50 years with breast cancer (HR = 1.67; 95% CI = 1.04 to 2.07)


For a woman in the general population, the risk of breast cancer is increased if she has a first-degree relative who was diagnosed with breast cancer at a young age or if she has more than one relative diagnosed with breast cancer (1,2). It is generally assumed that breast and ovarian cancers among women with a deleterious mutation in BRCA1 or BRCA2 are attributable primarily to the mutation; the extent to which a family history of cancer modifies the risks of these cancers is not known. In this prospective study, we modeled the influence of a family history of cancer on the risks of breast and ovarian cancer for 3011 women with a deleterious mutation in BRCA1 or BRCA2.

Eligible study subjects were identified from a cohort of women with a BRCA1 or BRCA2 mutation. Subjects were drawn from 33 centers in six countries that were participating in clinical research protocols. A woman was eligible for this study if molecular analysis had established that she was a carrier of a deleterious mutation in BRCA1 or BRCA2. Information was recorded on cancers in first- and second-degree relatives. The women were asked to report new diagnoses of cancer in themselves by completing a mailed questionnaire every 2 years. The family history for each subject was recorded as the numbers of first- and second-degree relatives with breast or ovarian cancer (ie, two subjects from the same family did not necessarily have the same family history). The study was approved by the ethics review board of Women’s College Research Institute, and all study subjects provided written informed consent.

For the estimation of breast cancer risk, a woman was potentially eligible for inclusion in this analysis if she was between 25 and 65 years at the time of completion of the baseline questionnaire, did not have breast cancer or a prophylactic mastectomy at or before baseline, and had been followed up for at least 2 years after baseline. These subjects were followed up until the development of breast cancer, prophylactic mastectomy, or the date of death or last follow-up, whichever occurred first. A total of 1964 women were eligible for this analysis. Cox proportional hazards models (implemented using SAS statistical software, version 9.1.3; SAS Institute, Cary, NC) were used for multivariable survival analysis. We confirmed that the data conformed to the proportional hazards assumption by using the supremum test in SAS statistical software. The hazard ratio (HR) for breast cancer was estimated for women with one or more affected first- or second-degree relatives with breast or ovarian cancer compared with women with no first- or second-degree relative with these cancers. The Cox proportional hazards model for breast cancer risk was adjusted for oophorectomy (yes vs no), age at baseline (in years) mutation (BRCA1 vs BRCA2), country of residence (Canada, United States, Poland, Austria, Italy, France), parity (0, 1, 2, 3, or ≥4 births) and breastfeeding history (yes vs no). For ovarian cancer risk estimation, eligibility criteria included age 25–65 years at baseline, no ovarian cancer diagnosis or prophylactic oophorectomy at baseline, and at least 2 years of follow-up. Subjects were followed up until the development of ovarian or fallopian tube cancer, prophylactic oophorectomy, death, or the date of last follow-up, whichever occurred first. A total of 2250 women were eligible for the ovarian cancer risk analysis. The hazard ratio for ovarian cancer was estimated for women with one or more affected first- or second-degree relatives with breast or ovarian cancer compared with women with no first- or second-degree relative with these cancers. The proportional hazards model for ovarian cancer was adjusted for age at baseline, mutation (BRCA1 vs BRCA2), country of residence, parity, oral
Table 1. Hazard ratios for breast cancer, given a family history of breast or ovarian cancer, in BRCA1 and BRCA2 mutation carriers*

<table>
<thead>
<tr>
<th>Variable</th>
<th>BRCA1 mutation carriers</th>
<th></th>
<th>BRCA2 mutation carriers</th>
<th></th>
<th>BRCA1 and BRCA2 mutation carriers combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate HR (95% CI)</td>
<td>P</td>
<td>Multivariable HR (95% CI)</td>
<td>P</td>
<td>Univariate HR (95% CI)</td>
</tr>
<tr>
<td>First-degree relatives with breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vs 0</td>
<td>1.29 (0.89 to 1.85)</td>
<td>.18</td>
<td>1.36 (0.94 to 1.98)</td>
<td>.10</td>
<td>0.70 (0.34 to 1.46)</td>
</tr>
<tr>
<td>≥2 vs 0</td>
<td>1.07 (0.74 to 1.54)</td>
<td>.72</td>
<td>0.96 (0.66 to 1.40)</td>
<td>.85</td>
<td>3.27 (1.23 to 8.70)</td>
</tr>
<tr>
<td>Per affected relative</td>
<td>1.19 (0.93 to 1.52)</td>
<td>.18</td>
<td>1.16 (0.90 to 1.49)</td>
<td>.25</td>
<td>1.80 (1.09 to 2.97)</td>
</tr>
<tr>
<td>/d-degree relatives diagnosed with breast cancer at age 50 years or younger</td>
<td></td>
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</tr>
<tr>
<td>1 vs 0</td>
<td>1.18 (0.80 to 1.74)</td>
<td>.39</td>
<td>1.20 (0.81 to 1.77)</td>
<td>.37</td>
<td>1.22 (0.52 to 2.86)</td>
</tr>
<tr>
<td>≥2 vs 0</td>
<td>1.56 (0.89 to 2.75)</td>
<td>.12</td>
<td>1.49 (0.84 to 2.64)</td>
<td>.18</td>
<td>3.25 (1.34 to 7.87)</td>
</tr>
<tr>
<td>Per affected relative</td>
<td>1.32 (0.96 to 1.85)</td>
<td>.12</td>
<td>1.21 (0.94 to 1.57)</td>
<td>.15</td>
<td>1.74 (1.09 to 2.78)</td>
</tr>
<tr>
<td>Second-degree relatives with breast cancer</td>
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</tr>
<tr>
<td>1 vs 0</td>
<td>0.96 (0.65 to 1.43)</td>
<td>.85</td>
<td>0.92 (0.62 to 1.37)</td>
<td>.68</td>
<td>0.63 (0.22 to 1.77)</td>
</tr>
<tr>
<td>≥2 vs 0</td>
<td>0.75 (0.44 to 1.26)</td>
<td>.27</td>
<td>0.65 (0.38 to 1.12)</td>
<td>.12</td>
<td>1.33 (0.58 to 3.06)</td>
</tr>
<tr>
<td>Per affected relative</td>
<td>0.88 (0.69 to 1.13)</td>
<td>.32</td>
<td>0.83 (0.65 to 1.06)</td>
<td>.14</td>
<td>1.20 (0.77 to 1.88)</td>
</tr>
<tr>
<td>First-degree relatives with ovarian cancer</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 vs 0</td>
<td>1.06 (0.73 to 1.52)</td>
<td>.09</td>
<td>1.01 (0.69 to 1.47)</td>
<td>.98</td>
<td>0.72 (0.29 to 1.76)</td>
</tr>
</tbody>
</table>
| **P**-values are from Cox proportional hazards models and are two-sided. HR = hazard ratio; CI = confidence interval.

* All family history–related variables were adjusted by age at baseline (years), oophorectomy (yes or no), BRCA1 or BRCA2 mutation, parity (0, 1, 2, or ≥3 live births, country of residence, and history of breastfeeding (yes or no).
multivariable survival analysis to estimate the extent to which the hazard ratio of breast cancer was influenced by family history, the risk of breast cancer for BRCA1 and BRCA2 mutation carriers combined increased by approximately 25% for each affected first-degree relative (HR per affected relative = 1.25; 95% confidence interval [CI] = 1.00 to 1.56; \( P = .09 \)) (Table 1). For BRCA1 and BRCA2 mutations carriers combined, the risk of breast cancer was associated with the number of first-degree relatives diagnosed with breast cancer at age 50 years or younger (HR per affected relative = 1.30; 95% CI = 1.04 to 1.63; \( P = .02 \)) but not with the number of first-degree relatives diagnosed with breast cancer after age 50 years (HR per affected relative = 1.08; 95% CI = 0.73 to 1.62; \( P = .70 \)) or with the number of second-degree relatives with breast cancer (HR per affected relative = 0.91; 95% CI = 0.66 to 1.33; \( P = .73 \)). A family history of ovarian cancer in a first-degree relative did not increase a woman’s risk of developing breast cancer (HR for ≥1 vs 0 affected relatives = 1.08; 95% CI = 0.73 to 1.62; \( P = .70 \)) or with the number of second-degree relatives with breast cancer (HR per affected relative = 0.91; 95% CI = 0.66 to 1.33; \( P = .73 \)). The impact of family history of breast cancer on breast cancer risk was greater for women with a BRCA2 mutation than for women with a BRCA1 mutation. For example, for each first-degree relative diagnosed with breast cancer at age 50 years or younger, the hazard ratio for breast cancer in BRCA1 mutation carriers increased by 1.21-fold (95% CI = 0.94- to 1.57-fold) and in BRCA2 carriers increased by 1.67-fold (95% CI = 1.04- to 2.69-fold).

However, the difference between these two hazard ratios was not statistically significant.

After a mean follow-up of 3.4 years, 91 women (4.0%) developed ovarian (n = 83) or fallopian (n = 8) cancer. In the following analyses, these two cancer sites were combined. In the survival analysis, ovarian or fallopian cancers in both first- and second-degree relatives were associated with an increased risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers combined after adjusting for age at baseline, BRCA mutation, country of residence, parity, breastfeeding history, tubal ligation, and oral contraceptive use (Table 2). Compared with BRCA1 mutation carriers with no first- or second-degree relative with ovarian cancer, those with two or more first- or second-degree relatives with ovarian cancer were statistically significantly more likely to develop ovarian cancer in the follow-up period. For women with a BRCA1 mutation, the risk of ovarian cancer increased by 61% for each first- or second-degree relative with fallopian or ovarian cancer (multivariable HR = 1.61; 95% CI = 1.21 to 2.14; \( P = .001 \)) (Table 2). Both first- and second-degree affected relatives contributed to the increased risk of ovarian or fallopian cancer. By contrast, the number of breast cancers in the family was not associated with the risk of ovarian or fallopian cancer. The number of events in BRCA2 mutation carriers was too small (n = 6) to generate a stable risk estimate.

We used the age-specific cancer rates for breast and ovarian cancer calculated in this study to estimate the penetrance of these cancers to age 70 years for women with BRCA1 and BRCA2 mutations. Among BRCA1 mutation carriers, the penetrance estimates for breast cancer for women with zero, one, and two or more first-degree relatives diagnosed with breast cancer at age 50 years or younger were 56%, 57%, and 72% (Figure 1, A). Among BRCA2 mutation carriers, the estimates were 38%, 46%, and 85%, respectively (Figure 1, B). Among BRCA1 carriers, the penetrance rates for ovarian cancer for women with zero, one, and two or more first- or second-degree relatives diagnosed with ovarian cancer were 39%, 55%, and 68%, respectively (Figure 1, C).

Our data indicate that, in women with a deleterious mutation in BRCA1 or BRCA2, a family history of cancer influences the risks of breast and ovarian cancer beyond the risks associated with the mutation alone. Among BRCA1 mutation carriers, the risk of breast cancer increased by approximately 20% for each first-degree relative with breast cancer, and among BRCA2 mutation carriers, the risk increased by approximately 70%. Having only a first-degree relative diagnosed with breast cancer at age 50 years or younger was associated with an increased risk of breast cancer in BRCA1 mutation carriers, whereas having both first- and second-degree relatives was associated with an increased risk of ovarian cancer. Compared with women with no affected relative, the risk of ovarian cancer in BRCA1 mutation carriers was increased by 1.6-fold if there was one relative with ovarian cancer and by 2.5-fold if there were two or more relatives with ovarian cancer.

We estimated the penetrance of breast cancer to age 70 years among women with BRCA1 mutations to be 58%. This estimate is somewhat less than that reported in a combined analysis of earlier studies (3), and may reflect the widespread use of oophorectomy, which is associated with a decreased risk of breast cancer (4,5). In this cohort, 38% of the women in the breast cancer cohort had an oophorectomy either at study entry or during the follow-up period. In BRCA1 mutation carriers, the lifetime risk of breast cancer varied from 56% to 72% depending on the number of first-degree relatives with breast cancer, and the lifetime risk of ovarian cancer varied from 40% to

Table 2. Hazard ratios for ovarian or fallopian cancer in BRCA1 mutation carriers*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate* HR (95% CI)</th>
<th>( P )</th>
<th>Multivariate* HR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>First- and second-degree relatives with ovarian cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vs 0</td>
<td>1.58 (0.96 to 2.60)</td>
<td>.07</td>
<td>1.50 (0.91 to 2.49)</td>
<td>.11</td>
</tr>
<tr>
<td>≥2 vs 0</td>
<td>2.53 (1.47 to 4.30)</td>
<td>&lt;.001</td>
<td>2.63 (1.50 to 4.63)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Per affected relative</td>
<td>1.59 (1.21 to 2.08)</td>
<td>&lt;.001</td>
<td>1.61 (1.21 to 2.14)</td>
<td>.001</td>
</tr>
<tr>
<td>First-degree relatives with ovarian cancer</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 vs 0</td>
<td>1.69 (1.09 to 2.63)</td>
<td>.02</td>
<td>1.35 (0.86 to 2.11)</td>
<td>.20</td>
</tr>
<tr>
<td>Second-degree relatives with ovarian cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 vs 0</td>
<td>1.75 (1.13 to 2.71)</td>
<td>.01</td>
<td>2.19 (1.38 to 3.47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>First-degree relatives with breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vs 0</td>
<td>0.95 (0.60 to 1.50)</td>
<td>.81</td>
<td>1.00 (0.63 to 1.58)</td>
<td>.99</td>
</tr>
<tr>
<td>≥2 vs 0</td>
<td>0.78 (0.39 to 1.59)</td>
<td>.50</td>
<td>0.44 (0.21 to 0.92)</td>
<td>.03</td>
</tr>
<tr>
<td>Per affected relative</td>
<td>0.90 (0.66 to 1.24)</td>
<td>.53</td>
<td>0.75 (0.55 to 1.01)</td>
<td>.06</td>
</tr>
</tbody>
</table>

* All family history–related variables were adjusted by age at baseline (years), parity (0, 1, 2, or ≥3 live births), history of breastfeeding (yes or no), tubal ligation (yes or no), oral contraceptive use (yes or no) and country of residence. \( P \) values are from Cox proportional hazards models and are two-sided. HR = hazard ratio; CI = confidence interval.
67%, depending on the number of ovarian cancers in the immediate family. It is important to note that these risks represent the average risks for the women in each category and may not be accurate for all women in each category. For example, a woman who has inherited a BRCA mutation from her father and who has no sister will be placed in the same category as a woman with multiple unaffected female first-degree relatives with the family BRCA mutation. Similarly, the ages of the unaffected women in the family may vary widely between families.

The principal strength of our study is its prospective design and the relatively large size of the cohort. Limitations include the short length of follow-up. In addition, although our penetrance estimates account for preventive surgery in the proband, we did not have information on risk-reducing measures in the relatives. Finally, in the risk calculations, we considered the number of affected relatives but not the number of unaffected relatives, and we did not have information about the mutation status of the relatives.

In conclusion, this cohort study supports the hypothesis that family-based factors other than the mutation itself will influence the risks of breast and ovarian cancers in BRCA1 and BRCA2 mutation carriers. These factors may include variations in modifying genes, and the search for these is now underway.

References

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