Abstract
The reasons for the high risk of contralateral breast cancer are not understood, although polygenic mechanisms have been suggested to be involved. The nationwide Swedish Family-Cancer Database was used to examine the interaction of the risks for contralateral and familial cancer. Relative risks were separately determined for contralateral and familial breast cancers, and these were tested for additive and multiplicative interactions. The Database contained information on 102,176 first breast cancers. Familial risk for breast cancer was 1.76 and the risk for contralateral breast cancer was 3.40, or 5.80 when extrapolated to two breasts. When women had a family history, the risk for contralateral breast cancer was remarkably high, 5.48, or 9.96 when the risk was extrapolated to two breasts, almost identical with 10.21, which was predicted by the multiplicative model. Although the data do not rule out polygenic mechanisms, they suggest that epigenetic imprinting events may be involved for the contralateral breast cancer. [Cancer Res 2007;67(3):868–70]

Introduction
Second primary breast cancers are increasing because the survival in the first primary cancer is improving and probably because early diagnostic methods, such as mammography, have been extensively used (1). If the causes of the second cancer were similar to those of the first one, the risks should be equal. However, they are higher and cannot be explained by treatment-related causes for contralateral cancer (2, 3), BRCA1/2 and CHEK2 mutations are likely to account for some contralateral breast cancers and, for others, polygenic models have been suggested (4–7). Because of the high risk, it would be important to better understand the causes of second breast cancers and how they may interact with other known risk factors of breast cancer, such as family history. In the present study, we use the nationwide Swedish Family-Cancer Database to investigate the interactions of family history and the risk for contralateral breast cancer, based on >100,000 first invasive breast cancers.

Materials and Methods
The Family-Cancer Database has been created by linking information from the Multigeneration Register, national censuses, Swedish Cancer Registry, and death notifications (8). Data on family relationships were obtained from the Multigeneration Register, whereby children born in Sweden in 1932 and later are registered with their biological parents as families. The Database was updated in 2004 to include the cancer cases from years 1958 to 2002. A first-degree family history considered mothers or sisters diagnosed with invasive breast cancer at any time between 1958 and 2002. Other risk factors of breast cancer, such as parity and age at first childbirth, were available in the Database. However, no data on stage or grade and treatment or prophylactic mastectomies were available; mastectomy rates would be expected to be very low.

The current risk estimates considered invasive contralateral breast cancers (primary cancer in the opposite breast) diagnosed any time after the first invasive breast cancer, judged to be independent primary tumors. Because laterality (left or right) of breast cancer was first coded in 1970 in the Cancer Registry, we restricted the study cohort to those diagnosed between 1970 and 2002. Person-years at risk were accumulated between diagnosis of the first and contralateral breast cancers, or death, emigration, or December 31, 2002, whichever came first. For immigrants, person-year calculations considered only their time in Sweden. Relative risks (RR) were calculated using Poisson regression analysis and adjusting for age, parity, and age at first childbirth (PROC GENMOD, SAS version 9.2, SAS Institute, Cary, NC). Collinearity was explored using the regression diagnostics of variance inflation factor (9); all variance inflation factor values were <2.5, suggesting that no correlations were noted between the independent variables. All independent variables were from registered sources containing no missing values. The risk for contralateral breast was extrapolated for two breasts using the formula \([RR - 1.0] \times 2 + 1.0\). The additive interaction was assessed as a sum of the two RR minus 1.0; the multiplicative interaction was the product of the two RRs (10). The underlying assumptions in this extrapolation are that the risk of contralateral breast cancer is independent of the first breast cancer and that one breast instead of two is at risk; these assumptions have been discussed by others (6). Confidence intervals (CI) for the estimated interactions were calculated by bootstrapping with 1,000 simulations (11).

Results and Discussion
According to the Database, a total of 102,176 women were diagnosed with breast cancer. The RR for the 90,090 women lacking a family history and contralateral breast cancer was used as a reference rate (1.00; Table 1). During the follow-up period, 7,103 women with a family history (6.96% of all breast cancer patients) developed breast cancer, showing an RR of 1.86 (95% CI, 1.74–1.98); among those without contralateral breast cancer, the RR was 1.76 (1.65–1.88). During the follow-up period, contralateral breast cancer was diagnosed in 5,495 (5.38%) women, giving an RR of 3.53 (3.24–3.84). The RR for contralateral breast was 5.48 (4.38–6.84) in women with a family history, and 3.40 (3.07–3.77) in women without a family history. Based on these data, the multiplicative interaction (contralateral risk \(\times\) family history) was 3.40 \(\times\) 1.76 = 5.98; the additive interaction was 3.40 + 1.76 – 1.00 = 4.16. The empirical risk for women with both risk factors was 5.48, thus much closer to the multiplicative than additive interaction.

Using the data in Table 1, we can extrapolate the risk of contralateral breast cancer in women without family history to two breasts by noting that the excess risk for the contralateral breast was 2.40 (3.40–1.00), translating to an excess of 4.80 for two breasts.
Table 1. RR for invasive familial and contralateral breast cancer according to the Poisson regression model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference rate</td>
<td>90,090</td>
<td>1.00</td>
</tr>
<tr>
<td>All women without family history and contralateral breast cancer</td>
<td>7,103</td>
<td>1.86 (1.74–1.98)</td>
</tr>
<tr>
<td>Familial risk for all women</td>
<td>6,591</td>
<td>1.76 (1.65–1.88)</td>
</tr>
<tr>
<td>Risk for contralateral breast in all women</td>
<td>5,495</td>
<td>3.53 (3.24–3.84)</td>
</tr>
<tr>
<td>Risk for contralateral breast in women without family history</td>
<td>4,983</td>
<td>3.40 (3.07–3.77)</td>
</tr>
<tr>
<td>Risk for contralateral breast in women with family history</td>
<td>512</td>
<td>4.58 (3.48–6.84)</td>
</tr>
</tbody>
</table>

NOTE: Data were adjusted for age, parity, and age at first birth. Boldface indicates that RR was statistically >1.00.

Table 2. Interactions of familial and contralateral breast cancer using different models

<table>
<thead>
<tr>
<th>Model</th>
<th>Observed*</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>True risk in this study</td>
<td>512</td>
<td>9.96 (9.68–10.31)</td>
</tr>
<tr>
<td>Multiplicative model</td>
<td>6,591 × 4,983</td>
<td>10.21 (10.11–10.41)</td>
</tr>
<tr>
<td>Additive model</td>
<td>6,591 + 4,983</td>
<td>6.56 (6.51–6.65)</td>
</tr>
</tbody>
</table>

*Observed number of cases.

and an RR of 5.80. Similarly, the risk for two breasts in women with a family history (RR 5.48 in Table 1) would equal to a RR of 9.96 for two breasts (true risk). The interactions were assessed in Table 2. The multiplicative interaction of 10.21 (5.80 × 1.74) gave an excellent fit, compared with the additive interaction of 6.56.

The results, based on a large number of cases, are in agreement with previous studies on the very high risk of contralateral breast cancer, particularly when considering that the risk is measured for a single breast (3, 5, 6). We and others have found the risk for contralateral breast to be essentially similar whether the follow-up was started immediately after the diagnosis of first cancer or within the first year after diagnosis (6). The present study was based on the Swedish Cancer Registry, which has clear instructions about the reporting of multiple primary malignancies; on reevaluation, 98% of second malignancies were found to be correctly classified (12). Besides, clonal concordance between the first and second breast cancers was reported to be nonsignificant in a Swedish study (13), suggesting that a vast majority of clinically diagnosed second breast cancers represent an independent disease. When the risk was translated to two breasts, it was 5.80 for women lacking a family history, clearly higher than the familial risk of 1.76. Clinical genetic counseling should particularly consider women with a family history, who had a risk of 5.48. The modeling favored a multiplicative interaction between family history and risk for contralateral breast cancer. However, some cautions need to be exercised in the interpretation, for reasons such as possible surveillance bias and effects of the wide use of adjuvant therapy with tamoxifen (14, 15).

The high risk for multiple primary cancers has been proposed to be a model for multistage carcinogenesis (16) and data in support of polygenic models have been presented for familial and bilateral breast cancer (7, 17). Multiple primaries arise in individuals who may have an unfortunate combination of risk genes; their relatives are lacking this combination and the familial risk is not evident. However, the very high risk for contralateral breast cancer and the lacking family history for most patients suggest that some individually determined factors, such as epigenetically regulated imprinting events, may play a role (18). Thus, important genes could be activated or silenced in the breast tissue of the patients but not in their relatives, in spite of gene sharing (19). Epigenetic mechanisms underlie even individual gene expression patterns between monozygotic twins (20). According to multistage models of cancer, two exposures that affect the same stage (sometimes interpreted as mutations in rate limiting genes) interact additively whereas those affecting different stages are thought to act multiplicatively (10). If this interpretation would apply to gene–gene interactions, the present data would imply that the genes or mechanisms responsible for familial and contralateral cancer risks would constitute a different set, plausibly the former being genetic and the latter epigenetic. An appealing aspect of this theory is that it can be tested by analyzing the methylation status of the tumors from the same individuals.

Acknowledgments

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References

Risks for Familial and Contralateral Breast Cancer Interact Multiplicatively and Cause a High Risk

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