Effect of BRCA1 and BRCA2 on the Association Between Breast Cancer Risk and Family History

Elizabeth B. Claus, Joellen Schildkraut, Edwin S. Iversen, Jr., Donald Berry, Giovanni Parmigiani

Background: The discovery of BRCA1 and BRCA2 has led to a reassessment of the association between family history of breast/ovarian cancer and breast cancer risk after controlling for carrier status for mutations in the BRCA1 and BRCA2 genes. We examined whether family history of breast cancer remains a predictive risk factor for this disease after carrier status for BRCA1 and/or BRCA2 mutations is taken into consideration. Methods: The data are from 4730 case subjects with breast cancer and 4688 control subjects enrolled in the Cancer and Steroid Hormone Study. The probability of being a BRCA1 and/or BRCA2 gene carrier was calculated for each woman. Among predicted noncarriers, logistic regression was used to assess the relationship (odds ratios and 95% confidence intervals [CIs]) between case or control status and family history of breast or ovarian cancer. Estimates of age-specific breast cancer risk are presented by predicted carrier status. Results: Among predicted noncarriers, case subjects were 2.06 times (95% CI = 1.69–2.50) and 1.24 times (95% CI = 1.17–1.32) more likely to report a first-degree or second-degree family history of breast cancer, respectively, than were control subjects. Case subjects were 1.99 times (95% CI = 1.63–2.44), 1.66 times (95% CI = 1.18–2.38), and 2.23 times (95% CI = 0.21–24.65) more likely to report an affected mother, sister, or both, respectively, than were control subjects. A family history of ovarian cancer was not statistically significantly associated with breast cancer risk. Noncarriers were predicted to have a lifetime risk of 9% of developing breast cancer compared with a 63% risk for carriers. Conclusions: Among women with a moderate family history of breast cancer, i.e., predicted noncarriers of BRCA1 and/or BRCA2 mutations, family history remains a factor in predicting breast cancer risk. In families with breast and ovarian cancers, the aggregation of these two cancers appears to be explained by BRCA1/BRCA2 mutation–carrier probability. [J Natl Cancer Inst 1998;90:1824–9]

It is well established that a family history of breast cancer is associated with an increased risk of developing breast cancer (1–10). In fact, among those variables that have been shown to bear a relationship with breast cancer, the greatest increase in risk, after controlling for age, has generally been associated with the presence of a positive family history of breast cancer (1–10). Published statistical estimates of the proportion of breast cancer in the general population that is likely to be attributable to an inherited mechanism range from approximately 6% to 19% (1–3,11–17), depending on the type of relative included in the calculation. When based solely on information obtained from first-degree relatives, this risk is widely estimated to be approximately 6%–7% (2,3,11), averaged across all ages at onset. The recent discovery of two genes associated with the development of breast cancer, BRCA1 and BRCA2 (18–25), along with preliminary laboratory-based prevalence data for these genes, allows investigators to begin to refine statistical estimates of the familial attributable risk of breast cancer.

At present, data suggest that a mutation in BRCA1 accounts for the majority (80%–90%) of families containing multiple case subjects with breast and/or ovarian cancer and approximately 45% of inherited breast cancer (12), whereas a mutation in BRCA2 is thought to account for approximately 35% of inherited breast cancer (21,22). Despite explaining a high proportion of breast and/or ovarian cancer incidence in high-risk families, current prevalence data on mutations in BRCA1 and BRCA2 indicate that the vast majority of women as well as the majority of case subjects with breast cancer in the United States are not carriers of mutations in these genes. Furthermore, most women with a family history of breast cancer are not members of high-risk families for breast and/or ovarian cancer, but instead have one or perhaps two family members affected with breast cancer. Therefore, the extent to which a positive family history of breast cancer remains a factor in the prediction of breast cancer risk outside high-risk families and after the estimated effects of mutations in BRCA1 and BRCA2 genes have been taken into account remains an important issue.

This report will examine whether a role for family history remains as a predictive risk factor for breast cancer once the effects of BRCA1 and BRCA2 have been taken into account.

Subjects and Methods

Data were obtained from the Cancer and Steroid Hormone Study, a multicenter, population-based, case–control study conducted by the Centers for Disease Control and Prevention. The dataset consists of 4730 case subjects aged 20–54 years with histologically confirmed breast cancer and 4688 control subjects. The case subjects were registered between December 1, 1980, and December 31, 1982, at eight Surveillance, Epidemiology, and End Results (SEER) Centers of the National Cancer Institute. Control subjects were selected through random-digit dialing and were matched by geography and 5-year age intervals to the case subjects. The eight centers include the cities and metropolitan areas of Atlanta (GA), Detroit (MI), San Francisco (CA), and Seattle (WA); the four urban counties of Utah; and the states of Connecticut, Iowa, and New Mexico. Case subjects with a history of breast cancer or a breast biopsy of unknown outcome were excluded from the study. In-home interviews were used to collect information on a wide variety of covariates for each of the case subjects and control subjects, including menstrual and pregnancy histories, use of oral contraceptives, and history of benign breast disease. In addition, case subjects and control subjects were interviewed about the occurrence of cancer in specific first-degree and second-degree female relatives. Cancer history in male relatives was not collected. A detailed description of the study may be found elsewhere (26).

The probability of carrying a mutation in BRCA1 or BRCA2 or both is calculated for each case subject and control subject (i.e., proband) by use of Bayes'
while containing sufficient numbers of relatives at risk. For this analysis, carrier probabilities were re-calculated to incorporate proband cancer status (i.e., whether the proband was herself affected and the age at onset or current age for the proband). This was done because this portion of the analysis focuses on risk to relatives rather than on risk to proband. The observed age-specific Kaplan–Meier risks of breast cancer in mothers and sisters of the probands were then computed. The analysis is done under the assumption that relatives of noncarriers are themselves likely to be noncarriers; hence, the risks associated with these women can be seen to represent those of the general noncarrier population. Among first-degree relatives of women predicted to be carriers of BRCA1 and/or BRCA2 mutations, approximately 50% would be themselves expected to be carriers under an autosomal dominant genetic model, whereas the remaining 50% would be expected to be normal homozygotes. (We assume that the homozygotes with mutations in both BRCA1 and BRCA2 genes are extremely rare and therefore not included in any calculations.) The observed Kaplan–Meier risk estimates for breast cancer seen for relatives of putative mutation carriers represent an average across the two groups of relatives. Therefore, the age-specific risks of breast cancer to carriers, R carriers , may be estimated as twice the Kaplan–Meier risks calculated among first-degree relatives of putative carriers, R0.00–0.01, minus the value for first-degree relatives of putative noncarriers, R0.00–0.01 (11, 29).

\[ R_{0.70–0.99} = (R_{\text{noncarriers}} + R_{\text{carriers}})/2 \]  

if \( R_{\text{noncarriers}} = R_{0.00–0.01} \) then

\[ 2 \times R_{0.70–0.99} = R_{0.00–0.01} = R_{\text{carriers}}. \]  

### RESULTS

Women with a joint probability less than or equal to 1% of carrying mutations in either BRCA1 or BRCA2 genes are defined as noncarriers. By use of this definition, 4337 (91.7%) of 4730 case subjects and 4447 (94.9%) of 4688 control subjects were predicted to carry neither BRCA1 nor BRCA2 mutations. Among case subjects diagnosed at the ages of 20–29 years, 10.5% were predicted to be carriers of either BRCA1 or BRCA2 mutations. This number decreased to 7.5% among women diagnosed between the ages of 50 and 54 years. Among women defined as noncarriers, the mean probability of being a BRCA1 mutation carrier was estimated at 6.8 \times 10^{-4}, with a range from 6.41 \times 10^{-6} to 9.8 \times 10^{-3}. The mean probability of being a BRCA2 mutation carrier was estimated at 3.2 \times 10^{-4}, with a range from 2.4 \times 10^{-9} to 6.5 \times 10^{-3}. Twenty-five percent of noncarriers versus 66% of carriers reported a family history of breast cancer. Approximately 2.2% of noncarriers versus 33% of carriers have a family history of ovarian cancer. The majority of women predicted to be noncarriers and who report a family history of breast cancer have a single first-degree or second-degree relative affected with breast cancer. This relative in general was younger in age for the carrier group than for the noncarrier group (44 years versus 56 years). Among women with both a mother and sister affected with breast cancer, the mean age of affected relatives for carriers versus noncarriers was calculated at approximately 46 years versus 62 years, respectively. For the remainder of this section, the terms “case subjects” and “control subjects” refer to the 4337 case subjects and 4447 control subjects defined as noncarriers.

Case subjects and control subjects did not differ with respect to religion, race, parity, or number of sisters. Case subjects were more likely than control subjects to be older (44.4 years compared with 43.8 years), younger at menarche, older at first live birth, premenopausal, and to have a history of benign breast disease.

Case subjects were 2.06 times (95% CI = 1.69–2.50) and 1.24 times (95% CI = 1.17–1.32) more likely to report a first-degree or second-degree family history of breast cancer, respectively, than were control subjects. These numbers did not change significantly when the model was adjusted for mutations in BRCA1 and BRCA2 gene carrier probability (both of which were nonsignificant) (Table 1) or for age, menopausal status, history of benign breast disease, and age at first full-term pregnancy (data not shown). Although a positive family history of breast cancer was significantly related to breast cancer risk among noncarriers, the same was not true for the relationship between a positive family history of ovarian cancer and breast cancer risk. Case subjects with breast cancer were 1.43 times (95% CI = 0.85–2.43) and 0.99 times (95% CI = 0.81–1.20) more likely to report a first-degree or second-degree relative with ovarian cancer than were control subjects. In fact, when BRCA2 and BRCA1 mutation carrier probabilities were included as covariates in the model to obtain adjusted ORs, family history of ovarian cancer had no significant role in predicting case or control status.

The risk of breast cancer by type of first-degree relative affected with breast cancer is presented in Table 2. Case subjects were 1.99 times (95% CI = 1.63–
Table 1. Risk of breast cancer in women unlikely to carry mutations in BRCA1 or BRCA2 genes, stratified by family history of breast cancer

<table>
<thead>
<tr>
<th>Family history*</th>
<th>Odds ratio (95% confidence interval)</th>
<th>Adjusted odds ratio† (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>First-degree only</td>
<td>2.06 (1.69–2.50)</td>
<td>1.90 (1.44–2.51)</td>
</tr>
<tr>
<td>Second-degree only</td>
<td>1.24 (1.17–1.32)</td>
<td>1.21 (1.13–1.29)</td>
</tr>
<tr>
<td>First-degree and second-degree</td>
<td>1.24 (1.09–1.42)</td>
<td>1.10 (0.91–1.33)</td>
</tr>
</tbody>
</table>

*Excludes 629 case subjects and 574 control subjects with unknown first-degree family history of breast cancer.
†Adjusted for BRCA1 and BRCA2 carrier probability.

2.44) and 1.66 times (95% CI = 1.18–2.38) as likely as control subjects to report an affected mother or sister, respectively. Women with both an affected mother and sister were at 2.23 times (95% CI = 0.21–24.65) the risk of developing breast cancer relative to women without such a family history, although there were only two case subjects and one control subject with such a family history. These values did not change significantly when adjusted for BRCA1 and BRCA2 carrier probability or for the above-mentioned environmental covariates, although the adjusted OR for women with both a mother and a sister affected is approximately half that of the unadjusted OR most likely due to instability of the estimate secondary to small sample size.

Case subjects diagnosed at ages 20–29 years, 30–39 years, 40–49 years, and 50–54 years were 5.30 times (95% CI = 0.94–29.75), 2.72 times (95% CI = 1.62–4.73), 2.13 times (95% CI = 1.59–2.86), and 1.70 times (95% CI = 1.24–2.32), respectively, more likely than control subjects to report a first-degree family history. These numbers did not differ significantly when adjusted for BRCA1 and BRCA2 mutation carrier probability with the exception of the age category 20–29 years for which small numbers (four case subjects and two control subjects with a positive family history) and multicol-linearity among the three variables (family history, BRCA1 and BRCA2 mutation carrier probability) prevent calculation of an adjusted OR. The risk of breast cancer by age at onset and laterality of affected first-degree relatives, neither of which was a significant risk factor, is presented in Table 3.

The estimated age-specific and cumulative risks of breast cancer for carriers and noncarriers are presented in Table 4. For noncarriers, i.e., first-degree relatives of probands with joint carrier probability of 0.00–0.01, the estimated risks match those generally reported for the U.S. female population, especially for the years 1980–1982 during which these data were collected. As expected, the estimated rates for carriers (calculated as twice the Kaplan–Meier estimates for first-degree relatives of probands with joint carrier probability of 0.70–0.99 minus the Kaplan–Meier estimates for first-degree relatives of probands with joint carrier probability of 0.00–0.01) are much higher at all ages and predict a very high penetrance for women who carry mutations in BRCA1 or BRCA2 genes.

Discussion

The extent to which the development of breast cancer may be attributed to inherited mutations in BRCA1 and BRCA2 genes remains a research area of intense investigation. Statistical and laboratory-based estimates of both carrier rates for such mutations and population attributable risk are being accrued in samples of affected and unaffected women. Using data from the Cancer and Steroid Hormone Study (CASH) in a previous analysis, Claus et al. (11) estimated the proportion of breast cancer attributable to inherited autosomal dominant genes to be approximately 33% of case subjects aged 20–29 years. This estimated risk de-

Table 2. Risk of breast cancer in women unlikely to carry mutations in BRCA1 or BRCA2 genes, stratified by first-degree family history of breast cancer

<table>
<thead>
<tr>
<th>Family history*</th>
<th>Odds ratio (95% confidence interval)</th>
<th>Adjusted odds ratio† (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Mother</td>
<td>1.99 (1.63–2.44)</td>
<td>1.55 (1.21–1.99)</td>
</tr>
<tr>
<td>Sister</td>
<td>1.66 (1.18–2.38)</td>
<td>1.21 (0.72–1.65)</td>
</tr>
<tr>
<td>Mother and sister</td>
<td>2.23 (0.21–24.65)</td>
<td>1.11 (0.09–13.77)</td>
</tr>
</tbody>
</table>

*Excludes 629 case subjects and 574 control subjects with unknown first-degree family history of breast cancer.
†Adjusted for BRCA1 and BRCA2 carrier probability.

Table 3. Risk of breast cancer by age at onset and laterality of breast cancer in relatives of women unlikely to carry BRCA1 or BRCA2

<table>
<thead>
<tr>
<th>Age at onset, y*</th>
<th>Odds ratio (95% confidence interval)</th>
<th>Adjusted odds ratio† (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>&lt;45</td>
<td>2.84 (1.84–4.50)</td>
<td>2.00 (0.99–4.08)</td>
</tr>
<tr>
<td>&gt;45</td>
<td>1.96 (1.47–2.62)</td>
<td>1.92 (1.54–2.39)</td>
</tr>
<tr>
<td>Laterality of cancer among first-degree relatives*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>2.21 (1.80–2.73)</td>
<td>1.94 (1.45–2.60)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>1.19 (0.68–2.08)</td>
<td>1.10 (0.56–2.17)</td>
</tr>
</tbody>
</table>

*Excludes 629 case subjects and 574 control subjects with unknown first-degree family history of breast cancer.
†Adjusted for BRCA1 and BRCA2 carrier probability.

Table 4. Estimated cumulative risk, % (standard error, %) of breast cancer for predicted carriers and noncarriers of mutations in BRCA1/BRCA2 genes

<table>
<thead>
<tr>
<th>Age at onset, y</th>
<th>Noncarriers</th>
<th>Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–9</td>
<td>0.0 (0.00)</td>
<td>4.3 (1.3)</td>
</tr>
<tr>
<td>10–19</td>
<td>0.2 (0.03)</td>
<td>19.8 (2.7)</td>
</tr>
<tr>
<td>20–29</td>
<td>0.8 (0.08)</td>
<td>41.3 (3.7)</td>
</tr>
<tr>
<td>30–39</td>
<td>1.6 (0.13)</td>
<td>50.4 (4.1)</td>
</tr>
<tr>
<td>40–49</td>
<td>2.7 (0.20)</td>
<td>52.8 (4.3)</td>
</tr>
<tr>
<td>50–59</td>
<td>5.1 (0.40)</td>
<td>62.8 (6.9)</td>
</tr>
<tr>
<td>60–69</td>
<td>8.8 (1.80)</td>
<td>62.8 (6.9)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>11.8 (2.90)</td>
<td>62.8 (6.9)</td>
</tr>
</tbody>
</table>

DISCUSSION

The extent to which the development of breast cancer may be attributed to inherited mutations in BRCA1 and BRCA2 genes remains a research area of intense investigation. Statistical and laboratory-based estimates of both carrier rates for such mutations and population attributable risk are being accrued in samples of affected and unaffected women. Using data from the Cancer and Steroid Hormone Study (CASH) in a previous analysis, Claus et al. (11) estimated the proportion of breast cancer attributable to inherited autosomal dominant genes to be approximately 33% of case subjects aged 20–29 years. This estimated risk de-
increased with age at onset to approximately 1.5% of case subjects aged 70 years or more. Using data from the Breast Cancer Consortium, Ford et al. (14) estimated that, in the general population, the proportion of breast cancer due to mutations in BRCA1 is 5.3% below the age of 40 years, 2.2% between the ages of 40 and 49 years, and 1.1% between the ages of 50 and 70 years. A third analysis (15), which combines data from three population-based, case–control studies of ovarian cancer (including the Cancer and Steroid Hormone Study), reports the proportion of case subjects with breast cancer due to BRCA1 and BRCA2 mutations to be 3.0% overall with a high of 11.2% among case subjects under the age of 30 years.

New laboratory data indicate that the proportion of breast cancer associated with BRCA1 may be higher than initially predicted by the Breast Cancer Consortium data but lower than that predicted by the CASH analyses (31–39). A study (32) of 80 women in whom breast cancer was diagnosed before the age of 35 reported that approximately 10% of these women carried germline alterations in the BRCA1 gene, whereas a second study (33) reported a mutation rate of 13% in a group of case subjects with breast cancer diagnosed before the age of 30. An analysis of women attending clinics that evaluate breast cancer risk (40) revealed a 7% rate of BRCA1 mutation in families with breast cancer but no ovarian cancer. Specific germline BRCA1 mutations, particularly the 185delAG mutation, have been identified at even higher rates among subsets of the general population, in particular young women or women of Ashkenazi Jewish background. Researchers have reported a 1% overall rate and a 21% prevalence rate among Jewish women diagnosed with breast cancer before the age of 40 (33–35). Similarly, a frequent germ line BRCA2 mutation (6174delT) has also been estimated at approximately 2.7% in case subjects with early onset of breast cancer (41). 1% in the Ashkenazi Jewish population (36), and approximately 8% in Ashkenazi case subjects with breast cancer diagnosed before the age of 42 years (37). New data collected with the use of intensive sequencing techniques reveal strikingly high carrier rates in a collection of women diagnosed with ovarian cancer or early onset breast cancer (40). In this series, 31% of women affected with unilateral breast cancer before age 50 and with at least one affected relative were found to carry either BRCA1 or BRCA2. Women with more extensive family history had even higher rates.

In general, a positive family history of breast cancer has been associated with a twofold to threefold increase in the risk of developing breast cancer. Previous analyses of these data (9), calculated before the discovery of BRCA1 and BRCA2 and using the entire dataset, reported that women with a first-degree or second-degree relative with breast cancer had relative risks of 2.3 and 1.5, respectively, compared with the adjusted risks of 2.0 and 1.2 reported here for the subset of women predicted to be noncarriers of BRCA1 or BRCA2. Women with both a mother and sister affected had a relative risk of 14 compared with 2.3 here. For all combinations of family history, the risks are reduced when predicted noncarriers are examined, markedly so for women with multiple affected relatives, although the CI in this instance is wide and actually includes the value reported by Sattin et al. (9). This reduction is expected in light of the fact that these women are more likely to be either BRCA1 or BRCA2 carriers. In these data, the majority (92%) of women who reported both a mother and at least one sister affected with breast cancer were predicted to have an increased probability of being carriers of mutations in BRCA1 or BRCA2 genes and hence were excluded from the analyses. As would be predicted by the model, noncarriers (i.e. the remaining 8% of women) with both a mother and sister affected with breast cancer were more likely to have relatives affected at older ages than were carriers, with the mean age of affected relatives for carriers compared with noncarriers calculated at approximately 46 years versus 62 years, respectively. In these data, the majority of women predicted to be noncarriers and who report a family history of breast cancer have a single first-degree or second-degree relative affected with breast cancer. Once again, this relative is younger for carriers than for noncarriers (44 years versus 56 years). It is interesting to note that even this relatively moderate family history of breast cancer remains significantly associated with breast cancer risk, despite the fact that most of these women are unlikely to carry either BRCA1 or BRCA2. A family history of ovarian cancer, however, appears to add no information to risk prediction once BRCA1 and BRCA2 carrier probability is known, matching existing laboratory data (42).

The estimated age-specific risks of breast cancer presented here for putative BRCA1 and BRCA2 mutation carriers compare reasonably well with those reported by other researchers (12–14,29,42), although the estimated lifetime risk of breast cancer reported here is relatively low. This appears to be due to the small numbers of older relatives among women predicted to be carriers (and the fact that probands in these data were from 20 to 54 years of age) and hence the presence of few affected older relatives from whom to obtain parameter estimates. A lifetime breast cancer risk of 63% for carriers in these data is compared with previously reported lifetime risks that range from 71% to 88%, depending on mutation type (12–14,42). As would be expected, given our inclusion of published penetrance estimates (12,29) as model parameters, our risk estimates are intermediate between those of Struwing et al. (29) and Easton et al. (12).

There are multiple interpretations for the results presented in this report, which include a variety of genetic, environmental, or statistical sources of variation. Genetic explanations include the fact that 1) mutations in noncoding regions of BRCA1 or BRCA2 or 2) other inherited, as yet unidentified, breast cancer genes, in addition to BRCA1 and BRCA2, may account for some portion of association between family history and breast cancer risk. Although BRCA1 and BRCA2 appear to explain the majority of inherited early onset breast cancer, a number of families with large numbers of case subjects with early onset breast cancer have been shown to be unlinked to BRCA1 and BRCA2 (16,21,25,39,43). Additional genes have already been implicated in the development of breast cancer (44–47); one study (44) associated one in 11 cancers of the breast in the general population with rare alleles of a minisatellite locus adjacent to the HRAS1 gene located on chromosome 11. In addition, the p53 gene has also been associated with the development of breast cancer in families characterized by the Li–Fraumeni syn-
The observed correlation of breast cancer status within families may also be explained by familial aggregation of environmental risk factors; i.e., family history may serve as a proxy variable for environmental factors such as socioeconomic status, diet, and age at first live birth that are correlated within families and that are themselves risk factors for the development of breast cancer. Correlations in breast cancer risk factors, such as age at menarche, with correlation coefficients of .2-.5, .25-.4, and .18-.65 have been reported, between random pairs of mothers and daughters, between sisters, and between twins, respectively (49). In addition, statistically significant associations in age at first pregnancy and age at menarche between related women have been reported (49). However, simulation studies (50,51) have shown that, even with complete correlation in exposure among family members, environmental variables must have relatively high values for relative risk for disease, i.e., on the order of 10-fold, to lead to even modest increases in recurrence risk among family members. Since the majority of environmental risk factors for breast cancer have been associated with increases on the order of twofold or less, it seems unlikely that simple familial clustering of these factors could entirely explain all of the remaining familial aggregation in breast cancer seen here, although it is likely to play some part in that aggregation.

In these data, accurate calculation of carrier probability depends on a correctly specified statistical model as well as on the carrier probability itself. Risk estimates of family history calculated here are slight overestimates of the true risk. Additional caveats for this work include the fact that, in these data, there is no information on male relatives as well as the fact that previous analyses of these data have indicated that the rates of breast and ovarian cancers are underreported in second-degree relatives. Both of these caveats may have led to underestimation of carrier probabilities for these women and hence to an overestimation of the remaining effect due to family history.

A final cautionary note must be added. Although the women in this analysis were defined as carriers and noncarriers on the basis of a generalized statistical model, these assignments may not hold true at the individual level. Women with low to moderate risk based on family history and ethnic background may still test positive for BRCA1 and BRCA2 mutations (40). The final determination of carrier status and the remaining role of family history will thus be a continually changing process as the collection of laboratory data proceeds.

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Notes

1Editor’s note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its data cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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