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 genes 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)1 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

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we wish to predict using an individual’s family his-
cancer status of the proband because this is the outcome 
12) BRCA2 prevalence estimates from Ford et al. 
original questionnaire. The model uses BRCA1 and 
rier probability also takes into account whether or 
unaffected female relatives. The calculation of car-
as well as the current age or age at death of any 
and the age at onset of any 
and the age at onset of any affected female relatives 
probability of being a gene carrier is calculated con-
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H BRCA1/BRCA2 mutation’’ and 
4 H M 
M P 
H M 
H M 
H M 
P(H) 
H M 
P(H|MI) = [P(H|M) × P(M)]/P(H). [1] 
The details of this model have been described pre-
27, 28). By use of this model, women with a joint prob-
ability of less than or equal to 1% of carrying mu-
tations in either BRCA1 or BRCA2 genes were de-
defined as noncarriers. In this analysis, first-degree 
family history was defined as a mother or sister af-
fected with breast cancer. Second-degree family his-
defined as a grandmother or aunt affected with 
breast cancer. Study subjects were defined to 
have unknown family history if the breast cancer 
status of all first-degree relatives was unknown. The 
initial portion of the statistical analysis included de-
scriptive statistics. The association between the risk 
of breast cancer and independent covariates was ex-
named by t tests and chi-squared tests. To assess the 
relative risk of breast cancer associated with a posi-
tive family history of breast cancer in women un-
likely to carry mutations in BRCA1 or BRCA2, lo-
gistic regression was used on predicted noncarriers 
to provide maximum likelihood estimates of the 
ods ratios (ORs) (adjusted and unadjusted) with 
95% confidence intervals (CIs) by use of the statis-
tical package PC-SAS version 6.11 (30). Women 
with affected first-degree relatives only, affected 
second-degree relatives only, or both affected first-
degree and second-degree relatives were compared, 
respectively, with women with no affected relatives. 
The risks are adjusted for BRCA1 and BRCA2 mu-
tation carrier probability and any significant (at a 5% 
type I error level) environmental covariates, includ-
ing age (years), race (white/black), parity, age at first 
live birth (years), menopausal status (premenopaus-
ul/postmenopausal), and history of benign 
breast disease (yes/no). 
To estimate the age-specific and cumulative risk of 
developing breast cancer among probable carriers 
and probable noncarriers, we divided case subjects 
and control subjects (i.e., the probands) into the fol-
lowing two groups by carrier probability: 1) noncar-
riers (defined as a proband having a carrier prob-
ability of 0.00–0.01) and 2) carriers (defined as a 
proband having a carrier probability of 0.70–0.99). 
The two probability groupings were selected in an 
effort to maintain relatively homogeneous groups 
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 fo-
cuses on risk to relatives rather than on risk to pro-
band. The observed age-specific Kaplan–Meier risks 
of breast cancer in mothers and sisters of the pro-
bands 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 a noncarrier population. Among 
first-degree relatives of women predicted to 
be carriers of BRCA1 and/or BRCA2 mutations, ap-
proximately 50% would be themselves expected to 
be carriers under an autosomal dominant genetic 
model, whereas the remaining 50% would be ex-
pected to be normal homoyzogotes. (We assume that 
the homoyzogotes 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. There-
fore, the age-specific risks of breast cancer to car-
riers versus noncarriers may be estimated twice the 
Kaplan–Meier risks calculated among first-degree relatives 
of putative carriers, 
R0.70–0.99 = (Rnoncarriers + Rcarriers)/2 [2] 
if Rnoncarriers = R0.00–0.01 then 
2 × R0.70–0.99 = R0.00–0.01 = Rcarriers. [3] 
RESULTS 
Women with a joint probability less 
than or equal to 1% of carrying mutations 
in either BRCA1 or BRCA2 genes are de-
defined as noncarriers. By use of this defi-
nition, 4337 (91.7%) of 4730 case sub-
jects and 4447 (94.9%) of 4688 control 
subjects were predicted to carry neither 
BRCA1 nor BRCA2 mutations. Among 
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 calcu-
lated 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 be-
nign breast disease, and age at first full-
term pregnancy (data not shown). Al-
though 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 muta-
tion carrier probabilities were included as 
covariates in the model (to obtain ad-
justed ORs), family history of ovarian 
cancer had no significant role in predict-
ing 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 sub-
jects 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.

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.

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 estimated 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 multicolinearity 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-
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 germline 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 be noncarriers of 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-
may lead to underestimating carrier probabilities for weak family histories. This is consistent with the belief that the penetrance functions currently used may be too high for families with weak histories. If this is true, then it is likely that the 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 BRCA1 and BRCA2 mutation 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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