Prevalence of BRCA1 and BRCA2 Mutations in Women Diagnosed With Ductal Carcinoma In Situ

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ellen Matloff, MS
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Context The distribution of BRCA1 and BRCA2 mutations in women diagnosed with noninvasive breast carcinoma is unknown.

Objective To estimate the BRCA1 and BRCA2 mutation prevalence in women with ductal carcinoma in situ (DCIS), unselected for age, family history, or ethnicity.

Design, Setting, and Participants The data were 369 DCIS cases diagnosed among female residents aged 20 to 79 years from the state of Connecticut between September 15, 1994, and March 14, 1996. These women were participants in a large population-based case-control study of breast carcinoma in situ. Telephone interviews were used to collect risk factor information and blood or buccal specimens were collected for BRCA1 and BRCA2 mutation testing.

Main Outcome Measures Prevalence of disease-associated mutations of BRCA1 and BRCA2 in women diagnosed with DCIS.

Results Three (0.8%) and 9 (2.4%) of 369 DCIS cases had disease-associated mutations in BRCA1 or BRCA2, respectively. One woman had a mutation in both genes (BRCA1 W321X and BRCA2 3398del5). Carriers were significantly more likely than noncarriers to report a first-degree (mother, sister, or daughter) family history of breast cancer (odds ratio [OR], 3.7; 95% confidence interval [CI], 1.1-12.4), as well as a personal history of ovarian cancer. In addition, carriers were more likely than noncarriers to be diagnosed at an early age (<50 years) (OR, 3.4; 95% CI, 1.0-11.7), as well as to report at least 1 first-degree relative diagnosed with breast cancer before 50 years (OR, 10.6; 95% CI, 3.0-37.0).

Conclusions Ductal carcinoma in situ is a part of the breast/ovarian cancer syndrome defined by BRCA1 and BRCA2, with mutation rates similar to those found for invasive breast cancer. These findings suggest that patients with breast cancer with an appropriate personal or family history of breast and/or ovarian cancer should be screened and followed according to high-risk protocols, regardless of whether they are diagnosed with in situ or invasive breast cancer.

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PREVALENCE OF \textit{BRCA1} AND \textit{BRCA2} MUTATIONS

Methods

The baseline case-control study population from which the women in this analysis are drawn includes all cases of female breast carcinoma in situ diagnosed among residents of Connecticut from September 15, 1994, to March 14, 1998. \cite{26-28} Cases were identified through the Rapid Case Ascertainment Shared Resource of the Yale Cancer Center, as well as the Connecticut Tumor Registry located in the Connecticut Department of Public Health, and were between the ages of 20 and 79 years at time of diagnosis. Controls were female Connecticut residents selected by random-digit-dialing methods and were frequency matched by 5-year age intervals to the cases. Study participants with a previous history of breast cancer and/or a breast biopsy of unknown outcome were excluded. The study, written consent forms, and questionnaire were approved by the Yale University School of Medicine Human Investigation Committee as well as by the Connecticut Department of Public Health Human Investigation Committee.

Cases approved for contact by their physicians and controls were interviewed by telephone about family history of cancer or ethnicity.

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Cases approved for contact by their physicians and controls were interviewed by telephone about family history of cancer, pregnancy and menstrual history, exogenous hormone use, demographics, and medical and screening history. Ethnicity/race was self-reported by study participants and used to provide risk estimates for each group. The final sample included 1068 case and 999 control participants, with overall response rates of 76% and 70%, respectively. All cases were identified by pathology report and confirmed via a uniform review by the study pathologist (D.C.). Further details of the study are presented elsewhere. \cite{26-28}

In 2000, funding was secured to re-contact participants of the initial study. Study participants who consented to the follow-up study were reinterviewed via telephone in the order in which they were first approached (by date of initial diagnosis). Case participants were asked to donate a blood or buccal specimen to be tested for mutations in the \textit{BRCA1} and \textit{BRCA2} genes. As part of genetic testing, women were offered 2 genetic counseling sessions, 1 before testing to provide information and obtain written informed consent, and a second to provide the results of testing. Study participants received genetic counseling at the Cancer Genetic Counseling Shared Resource of the Yale Cancer Center. At present, 975 cases have been recontacted and 777 (80%) have been reinterviewed. One hundred fourteen women (12%) have refused to participate, 60 (6%) are deceased, and 24 (2.5%) are too ill to participate. Among the cases who were reinterviewed, 55% agreed to undergo \textit{BRCA1} and \textit{BRCA2} testing, 30% decided not to undergo testing, and 15% were undecided regarding testing. Results are available for the first 422 cases; those results for the DCIS cases (n=369) are presented herein. The results for lobular carcinoma in situ (n=53) are not included.

Mutation testing was performed by Myriad Genetics (Salt Lake City, Utah) using direct gene sequencing as previously described. DNA was extracted for each consenting case participant from blood (n=296) or buccal (n=73) specimens. Aliquots of patient DNA were each subjected to polymerase chain reaction amplification. The amplified products were each directly sequenced in forward and reverse directions using fluorescent dye-labeled sequencing primers. Each genetic variant was independently confirmed by repeated analysis, including polymerase chain reaction amplification and sequence determination.

Statistical analyses included descriptive statistics and were computed using SAS version 8.1 (SAS Institute Inc, Cary, NC). t Tests, \(\chi^2\), and Fisher exact tests as well as unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were used to examine whether descriptive characteristics of the study population differed by study phase or between carriers and noncarriers. \(P<.05\) was considered statistically significant.

Results

A detailed presentation of the baseline characteristics of the initial case-control study population has been reported elsewhere, but key details will be reported herein for the sake of defining the population for whom our results are representative (Table 1). The initial case-control study matched well with the Connecticut Tumor Registry data with respect to race, age, histology, and socioeconomic status. More than 90% of the study participants were white, with other participants primarily black. This makeup matches the population of the state of Connecticut and also what is reported to the Connecticut Tumor Registry. \cite{31,32}

The characteristics of participants from the initial and follow-up studies are similar with the exception of age. Women who participated in the follow-up study were significantly younger than nonrespondents (mean, 54.9 vs 64.9 years, \(P<.001\)). Furthermore, among those women who participated in the follow-up study, those who agreed to undergo genetic testing were significantly younger at diagnosis than those who did not pursue testing (mean, 53.8 vs 58.4 years, \(P<.001\)). There were no differences across study phase by race, histology, Ashkenazi
Jewish ancestry, number of sisters and daughters, previous history of a benign breast biopsy, mammographic utilization, or, of interest, family history of breast or ovarian cancer.

Of the 369 women with DCIS tested to date, disease-associated mutations in BRCA1 and BRCA2 have been identified in 5 (0.8%) and 9 (2.4%) participants, respectively. One woman had a mutation in both BRCA1 and BRCA2 genes, both of which are disease-associated (BRCA1 W321X and BRCA2 S1630X) and 1 of which (BRCA2 Q1782K ) is not currently known to be deleterious. TABLE 2 lists the mutations in BRCA1 and BRCA2 (all of which result in protein truncation) detected in study participants by cancer history, age at diagnosis, ethnicity, and family history of breast and ovarian cancer. Ten mutation carriers identified themselves as white, and 1 identified herself as Asian (Chinese). One of 11 carriers reported being of Ashkenazi Jewish heritage; information on her cancer family history is limited by the fact that many of her relatives were killed during the Holocaust. A second woman was adopted and therefore did not know her ethnic heritage or cancer family history.

In addition to the 12 disease-associated mutations identified (in 11 women), genetic variants of uncertain significance, the majority of which represent amino acid substitutions, were observed in 43 women. Among this group of variants, it is not known at present if the substitution results in protein truncation; therefore, it is not known if the variant is disease-associated. Most of the variants have been previously associated with 1 or more deleterious or disease-associated mutations and therefore are probably themselves not deleterious mutations; however, in several instances the variant was first observed in these data. There was a statistically significant association between race and the presence of variants of uncertain significance, with 35 (10.1%) of 346 white cases, 6 (42.9%) of 14 black cases, 0 of 4 Hispanic cases, and 2 (66.7%) of 3 Asian cases having a variant.

The mean (SD) age at onset for BRCA1 and BRCA2 carriers was 49.3 (12.1) vs 54.2 (9.9) years (P=.11) for noncarriers. When age at onset was dichotomized at 50 years (average age at menopause in the United States), there was a statistical difference in the proportion of BRCA2 (P=.04) but not BRCA1 (P=.25) carriers by age with 1.6% and 4.6% of women younger than 50 years noted to be carriers of mutations in BRCA1 and BRCA2, respectively, vs 0.4% and 1.3% of women diagnosed at 50 years or older (TABLE 3). Carriers were more likely than noncarriers to report a first-degree (mother, sister, or daughter) family history of breast cancer (OR, 3.7; 95% CI, 1.1-12.4) and at least 1 first-degree relative diagnosed with breast cancer at an early age (<50 years) (OR, 10.6; 95% CI, 3.0-37.0). No carrier reported a first-degree family member affected with ovarian cancer, although the sample size was small, ovarian cancer relatively rare, and 2 of 11 carriers had unknown family history. Carriers were more likely than noncarriers to have a personal history of ovarian cancer (Fisher exact test, P<.001) with 2 (18.2%) of 11 carriers diagnosed with ovarian cancer (at 53 and 71 years) after their DCIS diagnosis (Table 2). Of the 11 carriers, 6 were noted to have comedo necrosis, a characteristic generally associated with an increased risk of progression to invasive breast carcinoma. Carriers and noncarriers did not differ with respect to number of sisters or daughters, age at first live birth, age at first menstrual period, history of benign breast biopsy, oral contraceptive use, hormone therapy use, race (white vs other), or mammographic utilization (ever vs never).

The 11 carriers received a variety of treatment plans (none of the women had their carrier status known at time of initial treatment). Three women underwent mastectomies without additional treatment, 1 woman underwent a mastectomy and received tamoxifen for several months and is currently taking anastrozole, 1 underwent lumpectomy only, 3 underwent lumpectomy...
and radiation therapy, and 3 underwent lumpectomy, radiation therapy, and tamoxifen. After a minimum follow-up of 5 years, 2 carriers reported an ipsilateral breast lesion (recurrence). Two women have reported a contralateral breast cancer and another 2 have developed ovarian cancer (5 and 7 years after the primary breast cancer). One woman reported a uterine cancer diagnosed before her primary breast cancer and a second woman reported a previous history of cervical cancer.

**COMMENT**
Our study is the first to our knowledge to examine the prevalence of **BRCA1** and **BRCA2** mutations in women diagnosed with DCIS and taken from a population-based study of breast carcinoma in situ. The **BRCA1** and **BRCA2** prevalence rates reported are similar to those observed in population-based studies of women diagnosed with IBC.2-4,6 Our estimates are contained within the confidence intervals of all of

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>BRCA1 Mutation</th>
<th>BRCA2 Mutation</th>
<th>Age at Onset, y</th>
<th>Ethnicity*</th>
<th>Cancer Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCIS/comedo necrosis</td>
<td>6174delT</td>
<td>3988del5</td>
<td>51</td>
<td>Ashkenazi</td>
<td>Mother and 2 maternal aunts with breast cancer at 45 y, 33 y, and age unknown, respectively; maternal grandmother’s sister with ovarian cancer, age unknown</td>
</tr>
<tr>
<td>DCIS, ovarian cancer</td>
<td>W321X</td>
<td>9254del5</td>
<td>46 (Breast)</td>
<td>Mixed</td>
<td>Sister and mother with breast cancer at 51 and 49 y (both <strong>BRCA2+</strong>); father dead at 46 y with “shoulder vs breast” mass</td>
</tr>
<tr>
<td>DCIS/comedo necrosis, ovarian cancer</td>
<td>3790ins4</td>
<td>66 (Breast)</td>
<td>71 (Ovarian)</td>
<td>British</td>
<td>Mother, 2 maternal aunts, and cousin with breast cancer at 78, 60, 35, and 50s y, respectively; maternal aunt and cousin with colon cancer, daughter with cervical cancer at 21 y and son with breast cancer at 50 y†</td>
</tr>
<tr>
<td>DCIS/comedo necrosis</td>
<td>S1630X, Q1782K†</td>
<td>46</td>
<td>White</td>
<td>Adopted, family history unknown</td>
<td></td>
</tr>
<tr>
<td>DCIS/comedo necrosis, uterine cancer</td>
<td>4075delGT</td>
<td>4078delC</td>
<td>56 (Uterine)</td>
<td>British</td>
<td>None known</td>
</tr>
<tr>
<td>DCIS</td>
<td>638delC</td>
<td>31</td>
<td>Mixed European</td>
<td>Sister with breast cancer at 43 y</td>
<td></td>
</tr>
<tr>
<td>DCIS (recurrence at 56 y)</td>
<td>2568insA</td>
<td>51</td>
<td>Mixed European</td>
<td>Mother with breast cancer at 42 y</td>
<td></td>
</tr>
<tr>
<td>DCIS/comedo necrosis (bilateral)</td>
<td>5385insC</td>
<td>31</td>
<td>Breast</td>
<td>Mother with breast cancer at 30 and 46 y</td>
<td></td>
</tr>
<tr>
<td>DCIS (bilateral)</td>
<td>L809X</td>
<td>46</td>
<td>Breast</td>
<td>Mother with endometrial cancer at 66 y, maternal aunt with breast cancer at 62 y, father with prostate cancer at 65 y</td>
<td></td>
</tr>
<tr>
<td>DCIS (recurrence at 49 y)</td>
<td>IVS17-1G&gt;C</td>
<td>34</td>
<td>Cervical</td>
<td>Stomach cancer in a maternal and paternal aunt</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.** Listing of **BRCA1** and **BRCA2** Disease-Associated Mutations in Study Sample

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>BRCA1 Mutation</th>
<th>BRCA2 Mutation</th>
<th>Age at Onset, y</th>
<th>Ethnicity*</th>
<th>Cancer Family History</th>
</tr>
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<td>Cervical</td>
<td>Stomach cancer in a maternal and paternal aunt</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.** Frequency of Mutations in Cases of Ductal Carcinoma In Situ by Age at Onset and Family History of Breast Cancer

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Age at Onset, y</th>
<th><em>Family History of Breast Cancer</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;50 (n = 131)</td>
<td>50 (n = 238)</td>
</tr>
<tr>
<td></td>
<td>None (n = 274)</td>
<td>Mother Affected (n = 57)</td>
</tr>
<tr>
<td>BRCA1</td>
<td>2 (1.6)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>6 (4.6)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Either</td>
<td>7 (5.4)</td>
<td>4 (1.7)</td>
</tr>
</tbody>
</table>

Abbreviation: DCIS, ductal carcinoma in situ.

*Self-reported by study participants.
*Proband’s mother-in-law had breast cancer at 69 years.
†Unknown if deleterious mutation.
these studies, with any variation in rate likely due to slight differences in the age distribution or ethnic composition of the study populations compared. One previous article reported BRCA1 and BRCA2 mutation prevalence rates in a series of in situ lesions, the rates from that article are higher than the rates we observed and ranged from 8.3% to 47.2% (depending on breast/ovarian cancer family history) for non-Ashkenazi Jewish women diagnosed with breast cancer before 50 years; however, the baseline population from which this group of women is drawn is unknown.

In our data, 1 woman was noted to have disease-associated mutations in both BRCA1 and BRCA2. This individual was diagnosed at an early age (37 years; she is the youngest carrier in our sample) and has 3 maternal family members who have breast cancer (at least 2 diagnosed younger than 45 years) as well as a maternal third-degree relative with ovarian cancer. None of her paternal relatives are known to have either breast or ovarian cancer; therefore, it is possible that both mutations were transmitted through the maternal line or that her father is a carrier who has not developed disease; at present neither parent has been tested. Although rare, studies exist of families and individuals with 2 or more mutations in BRCA1 and BRCA2. Generally, either one or both mutations are founder mutations described in the Ashkenazi-Jewish population. The genetic combination identified in these data (BRCA1 W321X and BRCA2 3398del5) remains one of the few studies of 2 nonfounder disease-associated mutations and the first in a woman diagnosed with DCIS; it is not known at present whether there is a functional link between these 2 mutations.

Although our data are drawn from the largest epidemiological study of breast carcinoma in situ to date, the statistical power to detect certain associations remains limited by sample size as well as the relative rarity of BRCA1 and BRCA2 mutations in the general population. The response rates for this study are consistent with those reported for other large case-control studies of cancer. However, at each stage of the follow-up study (interview, genetic testing) women who agreed to participate were younger on average by several years than were women who did not participate. This may be particularly important for estimating prevalence rates for BRCA1, given its reported inverse association with age (our rates may possibly overestimate the true rates). To date, 60 of the case participants are known to have died. If there is an association between BRCA1 and BRCA2 mutations and survival from DCIS, it is possible that our study may underestimate or overestimate the prevalence of these mutations due to the inclusion of women who are less or more likely to survive. Another potential source of bias is the fact that information on family history was obtained by interview with the case participant and was not confirmed by pathology report. However, because none of the case participants knew their carrier status at the time of the interview, it is unlikely that differences exist between carriers and noncarriers with respect to the reporting of cancer family history. With respect to measurement of the outcome variable (mutation prevalence), it is possible that some mutations may have been missed by the screening methods used (direct sequencing). In general, this method of screening may miss genomic rearrangements, which are thought to account for less than 10% of BRCA1 mutations and an even smaller proportion of BRCA2 mutations.

One of the most important findings of our study relates to the clinical management of women diagnosed with DCIS who are at increased risk of carrying a mutation in BRCA1 or BRCA2 by virtue of their personal or family cancer history. Our data suggest that previously reported risk factors in women with IBC, including family history of breast cancer, age at onset, as well as a personal history of ovarian cancer, may be helpful in predicting BRCA1 and BRCA2 carrier risk in women diagnosed with DCIS. Deleterious mutations in BRCA1 or BRCA2 carry increased risks of primary breast and ovarian cancer, as well as second breast and subsequent ovarian cancer. Before testing and counseling, the women in our study received a variety of counseling plans, ranging from none to biannual examinations. New screening strategies for women at high risk, including those with BRCA1 and BRCA2 mutations, have recently been updated by the American Cancer Society. The prevalence estimates presented herein as well as the health outcomes experienced by the women identified as carriers illustrate the importance of considering women diagnosed with DCIS as potential members of the inherited breast/ovarian cancer syndromes and highlight the need to test and follow DCIS cases with suggestive personal and family histories in the same manner as are women diagnosed with IBC.

Author Contributions: Dr Claus and Ms Petruzella had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Claus.

Acquisition of data: Claus, Petruzella, Matloff, Carter.

Analysis and interpretation of data: Claus.

Drafting of the manuscript: Claus.

Critical revision of the manuscript for important intellectual content: Claus, Petruzella, Matloff, Carter.

Statistical analysis: Claus.

Obtained funding: Claus.

Administrative, technical, or material support: Petruzella, Carter.

Study supervision: Claus, Petruzella, Matloff, Carter.

Financial Disclosures: None reported.

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REFERENCES