BRCA Mutations in Women with Ductal Carcinoma In situ

Karen Lisa Smith, Muriel Adank, Noah Kauff, Kelly Lafaro, Jeff Boyd, Johanna B. Lee, Clifford Hudis, Kenneth Offit, and Mark Robson

Abstract

Purpose: The strength of the association between ductal carcinoma in situ (DCIS) and BRCA mutations has not been defined.

Experimental Design: Mutation frequency was compared in three groups: (1) a prevalent series of women with DCIS, (2) an incident series of women with DCIS, and (3) a clinic-based series of women with DCIS referred for hereditary cancer risk assessment. In groups 1 and 2, limited to Ashkenazi Jewish (AJ) cases, mutation frequency was compared with that in age-matched AJ controls with invasive breast cancer (IBC).

Results: In group 1, 3 of 62 (4.8%) women with DCIS and 15 of 130 (11.5%) controls with IBC had BRCA1 mutations. In group 2, 0 of 58 (0%) women with DCIS and 6 of 116 (5.2%) controls with IBC had BRCA1 mutations [combined odds ratios (OR) in groups 1 and 2: 3.64, 95% confidence interval (95% CI), 1.06-12.46; P = 0.04]. In group 3, deleterious mutations were identified in 10 of 79 (12.7%) probands with DCIS, similar to the frequency in IBC probands. In group 3, mutations were associated with family history of ovarian cancer (OR, 13.35; 95% CI, 2.48-71.94; P = 0.003) or early onset breast cancer (OR, 16.23; 95% CI, 1.68-157.01; P = 0.02) but not with AJ ethnicity or age at diagnosis.

Conclusions: BRCA mutations were less frequent in women with DCIS not selected for family history or age at diagnosis than in women with IBC. Nonetheless, mutations were found in a significant proportion of women with DCIS who presented for hereditary risk assessment.

Carriers of BRCA1 and BRCA2 mutations are at an increased risk for multiple malignancies, especially breast and ovarian cancer. Cumulative breast cancer risks by age 70 are estimated to be 65% for BRCA1 and 45% for BRCA2 mutation carriers. Only 5% to 10% of cases of invasive breast cancer (IBC) result from an autosomal dominant predisposition (1), but the prevalence of BRCA mutations is higher in young women and in women from populations with founder mutations. For example, 1 in 40 Ashkenazi Jewish (AJ) individuals carry a founder mutation in the BRCA1 or BRCA2 gene (2). Among AJ women diagnosed with breast cancer before the age of 40, 13% to 43% carry BRCA mutations (3–5).

The incidence of ductal carcinoma in situ (DCIS), which is usually asymptomatic, has risen dramatically over the past 20 years due to the widespread use of screening mammography. The association of BRCA mutations with IBC is well established, but some controversy exists regarding whether DCIS should be considered a component of the BRCA-associated hereditary breast-ovarian cancer syndrome. An early epidemiologic study reviewing 36 families with BRCA1 mutations found only four cases of DCIS (6). Subsequent studies evaluating pathologic specimens from women with sporadic and BRCA mutation–associated IBC found less DCIS associated with the invasive cancers in the BRCA1 mutation carriers than the sporadic cases (7–9). These studies have led to the suggestion that the preinvasive phase may be shortened or even absent in hereditary breast cancers, particularly those associated with BRCA1 mutations (8).

The identification of DCIS in risk-reducing mastectomy specimens from women with BRCA mutations and in biopsies done in response to abnormal screening studies in BRCA mutation carriers have led investigators to reconsider DCIS as a component of the hereditary breast-ovarian cancer syndrome (10–16). Claus et al. identified BRCA mutations in 3.3% of women with DCIS in a large, population-based study (17). This mutation prevalence is similar to that described in population-based ascertainment of women with IBC. Other studies have also suggested that DCIS may be a component of the syndrome, although less characteristic than invasive disease. In Frank et al.’s description of genetic test results from 10,000 consecutive individuals, BRCA mutations were found in 13% of women with DCIS prior to age 50. Mutations were twice as prevalent in young women with IBC (18). Hwang et al. found no difference in the prevalence of DCIS (with or without IBC) in mutation carriers and high-risk noncarriers, although the number of women with DCIS only was small (19).

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To further characterize the association between DCIS and BRCA mutations, we compared the frequency of BRCA mutations in nonoverlapping prevalent, incident, and clinic-based cohorts of women with DCIS and IBC. This approach allowed a comparison of mutation rates in groups not selected for genetic testing on the basis of either early diagnosis or family history (FH), and those referred for genetic risk assessment on the basis of these same variables.

### Materials and Methods

BRCA mutation prevalence was determined in three groups of women. The first two groups were prevalent (group 1) and incident (group 2) hospital-based ascertainment of AJ women with DCIS. Group 3 was a clinic-based ascertainment of AJ and non-AJ women with DCIS who presented to a hereditary cancer risk assessment service. All ascertainment and deidentification procedures were approved by the Memorial Sloan-Kettering Cancer Center Institutional Review Board.

Cases for group 1 were 120 Jewish women with DCIS drawn from a sample of cancer patients receiving follow-up care at Memorial Sloan-Kettering Cancer Center ascertained without regard to age at diagnosis or FH. DNA for genotyping was extracted from lymphocytes from residual material remaining after routine blood tests and annotated with cancer type, age at diagnosis, and religion (self-reported). At Memorial Sloan-Kettering Cancer Center, >90% of individuals reporting Jewish religious preference were of Eastern/Central European (Ashkenazi) descent, thus all self-identified Jewish subjects were considered to be AJ. Cases associated with invasion or microinvasion were excluded, leaving a total of 66 women with pure DCIS eligible for study. Each case was age-matched (within ± 3 years) to two female Jewish controls with IBC from the same ascertainment. Pathology reports were reviewed. Two cases with DCIS on the initial biopsy were found to have invasive disease at definitive surgery, and were excluded, leaving 64 DCIS cases and 132 IBC controls. Samples were irreversibly deidentified and genotyped for the Ashkenazi founder mutations (BRCA1 185delAG, BRCA1 5382insC, BRCA2 6174delT) as previously described (20). Genotyping failed for four samples (two DCIS, two IBC), leaving 62 DCIS cases and 130 IBC controls. Cases and controls for group 2 were drawn from a prospective ascertainment of women undergoing surgery at Memorial Sloan-Kettering Cancer Center between May 2001 and December 2004 for a new diagnosis of breast cancer, ascertainment without regard to age at diagnosis or FH. The study database was queried and 58 Jewish women enrolled with a diagnosis of pure DCIS were selected. No woman in group 2 was a member of group 1. Each of these DCIS cases was age-matched (within ± 4 years) to two Jewish women from the same ascertainment whose surgeries yielded IBC. Pathology reports were again reviewed. Samples were irreversibly deidentified and genotyped for the AJ founder mutations as described.

Group 3 was a clinic-based ascertainment of women evaluated by the Clinical Genetics Service at Memorial Sloan-Kettering Cancer Center between January 1995 and December 2005. In this interval, 104 female probands (AJ and non-AJ) with DCIS, and 2,002 individuals with IBC presented for hereditary cancer risk assessment and subsequently underwent genetic counseling and testing. All subjects were participants in Institutional Review Board–approved follow-up studies of women at hereditary risk for cancer and consented to genetic testing after appropriate pretest counseling. Women were excluded from consideration as a case if a pathology report confirming DCIS was unavailable or if the report indicated definite invasion or microinvasion. In addition, women with a history of IBC or ovarian cancer (OC) prior to their diagnosis of DCIS were excluded. A total of 79 probands with pure DCIS remained for analysis. Factors potentially associated with BRCA mutations were assessed, including age at diagnosis of DCIS, FH of breast cancer or OC in at least one first and/or second degree relative, and ethnicity (AJ versus non-AJ). FH of breast cancer was considered to be early onset if the affected family member was diagnosed at age ≤50. All women who self-identified Jewish maternal and/or paternal descent were considered to be AJ. Probands for whom ethnicity was unknown were grouped with non-AJ probands for the analysis. Founder mutation analysis seeking the three common AJ founder mutations was done for AJ women. Full sequence analysis (usually with rearrangement panel testing) was offered to all AJ probands without founder mutations, and was done in 31%. Except for one non-AJ woman who underwent limited testing, genetic testing for all non-AJ probands involved full sequence analysis. For the statistical analysis, probands with genetic variants of uncertain significance were grouped with probands without mutations.

The t test was used to compare means and Fisher’s exact test was used to compare proportions. Odds ratios (OR) were calculated to assess the strength of the relationship between DCIS and BRCA mutations. Univariate and multivariate logistic regression analyses were done to identify factors predictive of mutations in the DCIS patients. Variables significant in univariate analyses were included in the multivariate model. P < 0.05 was considered significant. All statistical tests were two-sided. Statistics were done using Intercooled Stata Version 8.2 (Stata Corp.).

### Results

**Nested case-control studies of unselected AJ women with DCIS.** Results from groups 1 and 2 are displayed in Table 1. For group 1, mean age at diagnosis did not differ between the DCIS cases and IBC controls (DCIS, 56.5; IBC, 56.7; P = 0.90; overall age range, 23-85). AJ founder mutations were identified in 3 DCIS cases (4.8%) and 15 IBC controls (11.5%; P = 0.19). Mean age was younger among those with mutations than those without mutations (mutation, 50.6; no mutation, 57.2; P = 0.02). Of the DCIS patients with mutations in group 1, two occurred in BRCA2 and one occurred in BRCA1.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of BRCA mutations in DCIS cases</th>
<th>No. of BRCA mutations in IBC cases</th>
<th>P*</th>
<th>OR 1 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unselected ascertainment</td>
<td></td>
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</tr>
<tr>
<td>Group 1: prevalent cases</td>
<td>3/62 (4.8%)</td>
<td>15/130 (11.5%)</td>
<td>0.19</td>
<td>2.57 (0.71-9.21)</td>
</tr>
<tr>
<td>Group 2: incident cases</td>
<td>0/58 (0%)</td>
<td>6/116 (5.2%)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Groups 1 and 2 combined</td>
<td>3/120 (2.5%)</td>
<td>21/246 (8.5%)</td>
<td>0.04</td>
<td>3.64 (1.06-12.46)</td>
</tr>
<tr>
<td>Clinic-based ascertainment</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Group 3 compared with all IBC</td>
<td>10/79 (12.7%)</td>
<td>282/2002 (14%)</td>
<td>0.87</td>
<td>1.11 (0.58-2.15)</td>
</tr>
<tr>
<td>Group 3 compared with IBC at age &lt;50</td>
<td>222/1281 (17%)</td>
<td>0.44</td>
<td>1.37 (0.70-2.65)</td>
<td></td>
</tr>
</tbody>
</table>

*P value for Fisher exact test comparing proportions of DCIS cases and IBC controls with BRCA mutations.

1 Odds of mutation in IBC controls compared with DCIS cases.
Table 2. Characteristics of probands with DCIS presenting for hereditary cancer risk assessment (group 3)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish</td>
<td>42/79 (53.2)</td>
</tr>
<tr>
<td>Age ≤50 at diagnosis of DCIS</td>
<td>56/79 (70.9)</td>
</tr>
<tr>
<td>FH of breast cancer (first or second degree)</td>
<td>61/79 (77.2)</td>
</tr>
<tr>
<td>FH of early onset breast cancer (first or second degree)</td>
<td>36/79 (45.6)</td>
</tr>
<tr>
<td>FH of ovarian cancer</td>
<td>14/79 (17.7)</td>
</tr>
</tbody>
</table>

Mean age also did not differ between the DCIS cases and the IBC controls in group 2 (DCIS, 60.1; IBC, 59.8; P = 0.91; overall age range, 39-88). No BRCA mutations were identified among the DCIS cases in group 2. AJ founder mutations were identified in six IBC controls (5.2%) in group 2 (P = 0.18). Mean age was not significantly younger among those with mutations than those without mutations (mutation, 53.2; no mutation, 60.1; P = 0.15).

The overall prevalence of founder mutations in the combined ascertainment of AJ women with DCIS not selected on the basis of FH or age at diagnosis (groups 1 and 2) was 3 of 120 (2.5%). Founder mutations were 3.64 times more likely to be identified in age-matched IBC controls than in DCIS cases [combined OR, 3.64; 95% confidence interval (95% CI), 1.06-12.46; P = 0.04].

Clinic-based ascertainment. The characteristics of the 79 DCIS probands in the clinical ascertainment are displayed in Table 2. Of note, 45.6% had a FH of early onset breast cancer and 17.8% had a FH of OC. The mean age of diagnosis of DCIS was 46.9 (range, 24-75).

Among the 79 probands, 10 were found to have deleterious BRCA mutations (12.7%) and 2 were found to have variants of uncertain significance (2.5%). Seven of the 10 deleterious mutations identified were in BRCA1, whereas 3 were in BRCA2. Deleterious mutations were identified in 5 of 42 AJ probands (11.9%) and in 5 of 37 non-AJ probands (13.5%; P = 1.00). Deleterious mutations were identified in 7 of 56 probands ≤50 years old (12.5%) and in 3 of 23 probands >50 years old (13.0%) at diagnosis of DCIS (P = 1.00). In comparison, deleterious mutations were identified in 282 (14%) of 2,002 women with IBC seen during this same period, including 222 of 1,281 (17%) of those with IBC before age 50 (Table 1).

Table 3 displays the proportions of probands with BRCA mutations based on FH, stratified by ethnicity and by proband age at diagnosis. The groups with the highest mutation prevalence were those with a FH of OC and/or early onset breast cancer. Among probands with family histories of both OC and early onset breast cancer, mutations were identified in 75%. No mutations were identified in non-AJ probands who did not have a FH of breast cancer and/or OC. Only one proband without a FH of breast cancer or OC, an AJ woman diagnosed at age 40, was found to carry a mutation. A FH of later onset (>50 years) breast cancer without a history of either early-onset BC or OC was not associated with mutations.

Univariate logistic regression analysis identified FH of OC and FH of early onset breast cancer as factors predictive of mutation status among the DCIS probands in the clinical ascertainment. Ethnicity and proband age at diagnosis were not predictors of mutation status (P = 0.83 and 0.95, respectively). In multivariate analysis, a FH of OC was associated with a 13-fold increase in the likelihood of identifying a mutation (OR, 13.35; 95% CI, 2.48-71.94; P = 0.003) and a FH of early onset breast cancer was associated with a 16-fold increase in the likelihood of identifying a mutation (OR, 16.23; 95% CI, 1.68-157.01; P = 0.02; Table 4).

Discussion

The present study suggests that a diagnosis of IBC is more suggestive of an underlying BRCA mutation than a diagnosis of DCIS. In the nested case-control studies of AJ women with DCIS not selected for FH or age at diagnosis, mutations were identified in 2.5%, significantly lower than the frequency of mutations in age-matched controls with invasive cancer. Indeed, the prevalence of mutations in AJ women with DCIS was similar to the 1.8% (62 of 3,434) observed by Hartge et al. in AJ volunteers without a diagnosis of breast or ovarian cancer (21). This suggests that AJ founder mutations are not associated with an increased risk of DCIS in women who are not selected for early-onset disease or FH of breast or ovarian cancer, but the small sample size and lack of formal age-matching limits the ability to reach a definitive conclusion. In particular, very few women with early-onset DCIS were included in the unselected ascertainment, reflecting the usual age distribution of this disease.

Table 3. Proportion of probands with DCIS in the clinical ascertainment with BRCA mutations, based on FH and stratified by ethnicity and by age at diagnosis of DCIS

<table>
<thead>
<tr>
<th>FH*</th>
<th>All probands with DCIS (%)</th>
<th>AJ probands with DCIS (%) †</th>
<th>Non-AJ probands with DCIS (%) †</th>
<th>Probands age ≤50 at diagnosis of DCIS (%) †</th>
<th>Probands age &gt;50 at diagnosis of DCIS (%) †</th>
</tr>
</thead>
<tbody>
<tr>
<td>No FH of breast cancer or ovarian cancer</td>
<td>1/17 (5.9)</td>
<td>1/11 (9.1)</td>
<td>0/6 (0)</td>
<td>1/10 (10)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>FH history of breast cancer in women age &gt;50, no FH of OC</td>
<td>0/20 (0)</td>
<td>0/10 (0)</td>
<td>0/10 (0)</td>
<td>0/15 (0)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>FH of breast cancer in women age ≤50 (with or without FH of breast cancer in women age &gt;50), no FH of OC</td>
<td>3/28 (10.7)</td>
<td>1/14 (7.1)</td>
<td>2/14 (14.3)</td>
<td>3/23 (13)</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>FH of OC, with or without FH of breast cancer</td>
<td>6/14 (42.9)</td>
<td>3/7 (42.9)</td>
<td>3/7 (42.9)</td>
<td>3/8 (37.5)</td>
<td>3/6 (50)</td>
</tr>
</tbody>
</table>

*FH in first- and/or second-degree relatives.
† All probands are listed in two subgroups (AJ or non-AJ and ≤50 or >50).
In the clinic-based ascertainment of women with DCIS, in whom the mean age at diagnosis was lower, and a FH of OC and/or early onset breast cancer was common, BRCA mutations were identified in 12.7% of probands (11.9% of AJ and 13.5% of non-AJ women). This is consistent with the frequency of 13% in women with DCIS diagnosed before age 50 in a retrospective analysis of 10,000 consecutive patients referred for genetic testing (18), and slightly less than the 17% (222 of 1,281) prevalence of BRCA mutations observed among women with IBC before age 50 referred for genetic testing at our institution during this same period. This comparison is limited by several factors. Pathology reports confirming invasive disease were not available for all of the women with IBC, and misclassification bias could affect the comparison. Also, during the interval covered by this study, AJ ethnicity was slightly less common in women undergoing testing for IBC at our institution (49%) than in the DCIS cases reported here (53%). AJ ethnicity was not associated with an increased prevalence of mutations among the women with DCIS, but an IBC cohort with fewer AJ women would be expected to have a lower mutation prevalence than one with a greater proportion of Jewish women, narrowing the apparent differential between DCIS and IBC. A definitive comparison of frequencies of BRCA mutations in DCIS and IBC in clinic-based series would require matching for age at diagnosis, ethnicity, and pedigree structure, as well as limiting ascertainment to kindreds that have not previously been tested for BRCA mutations.

BRCA mutations may have been more prevalent in the clinic-based ascertainment because of increased breast cancer screening in women with family histories of breast or ovarian cancer. Adem et al. have suggested that all stages of carcinogenesis occur in BRCA mutation–associated breast cancer, but that the process occurs more quickly than in sporadic breast cancer (22). This would lead to a shorter in situ phase and, possibly, to a lower likelihood of identifying in situ cancers with conventional screening techniques and intervals. Women referred for genetic risk assessment, many of whom have a FH consistent with hereditary breast-ovarian cancer syndrome, may participate in more frequent screening than women in the general population. This more frequent screening may identify BRCA–associated breast cancers in their relatively short in situ phase. In women without a FH that would prompt genetic risk assessment, undergoing less intensive breast cancer screening, BRCA–associated cancers may progress to invasion before detection. Alternatively, the DCIS lesions identified in women in the clinical ascertainment may be incidental, and not related to the underlying genetic predisposition.

FH factors predictive of BRCA mutation status in DCIS probands referred for genetic risk assessment were identified in this study. Multivariate analysis revealed that FH of OC and early onset BC were strongly predictive of mutation status (OR, 13.35 and 16.23, respectively). These risk factors are similar to those previously reported both for IBC and DCIS, and are also associated with mutation detection in unaffected women. Frank et al. identified FH of OC and early onset breast cancer as risk factors for BRCA mutations among probands with IBC and DCIS (18), as have many other investigators. Claus et al. found that DCIS cases with BRCA mutations were more likely to have personal histories of OC and FH of early onset breast cancer (17).

The present study has certain limitations. For the nested case-control studies, prevalent and incident ascertainment were combined to improve power. As survival from DCIS approaches 100%, there is no obvious reason to suspect significant differences in mutation prevalence between incident and prevalent cohorts, but larger sample sizes would be required to exclude such an effect. FH information was not available for the unselected groups, which also limits the conclusions that can be drawn. In the clinical ascertainment, some of the AJ probands only underwent testing for AJ founder mutations whereas others also underwent full sequencing. It is possible that some nonfounder mutations were missed in the probands for whom full sequencing was not done; however, the number of such mutations is unlikely to be high enough to affect the conclusions. Finally, self-report was used to determine FH, a practice which may be subject to error. This study indicates that women presenting for hereditary risk assessment with a personal history of DCIS may be found to carry BRCA mutations, particularly if they have significant family histories of ovarian cancer or early-onset breast cancer. The findings support, but do not prove, the presence of an in situ phase of carcinogenesis in the development of at least some BRCA–associated breast cancers. This emphasizes the potential benefit of screening in mutation carriers, which may identify cancers while in an in situ phase. The comparatively lower prevalence of mutations in women with DCIS compared with those with invasive cancer suggests that a preinvasive phase, if it exists, may be shortened in a significant proportion of BRCA–associated breast cancers. Clinical trials to evaluate the benefit of screening at more frequent (e.g., semiannual) intervals may address this possibility.

### Acknowledgments

We thank Dr. Jeffrey Struwing for providing data from the Washington Ashkenazi Survey.

<table>
<thead>
<tr>
<th>Predictors of BRCA mutations</th>
<th>Unadjusted OR (95% CI) [P value]</th>
<th>Adjusted OR* (95% CI) [P value]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish</td>
<td>0.86 (0.23-3.26) [0.83]</td>
<td>Not included</td>
</tr>
<tr>
<td>FH+ of breast cancer</td>
<td>2.94 (0.35-24.94) [0.32]</td>
<td>Not included</td>
</tr>
<tr>
<td>FH+ of breast cancer in women age ≤50</td>
<td>14.00 (1.68-116.85) [0.02]</td>
<td>16.23 (1.68-157.01) [0.02]</td>
</tr>
<tr>
<td>Proband age ≤50 at DCIS diagnosis</td>
<td>0.95 (0.22-4.06) [0.95]</td>
<td>Not included</td>
</tr>
<tr>
<td>FH+ of ovarian cancer</td>
<td>11.44 (2.65-49.45) [0.001]</td>
<td>13.35 (2.48-71.94) [0.003]</td>
</tr>
</tbody>
</table>

*Only variables significant in univariate analysis were included in multivariate model.

* FH in first- and/or second-degree relatives.
References


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