Prevalence of BRCA1 and BRCA2 Mutations in Women with Breast Carcinoma In Situ and Referred for Genetic Testing

Michael J. Hall1, Julia E. Reid2, and Richard J. Wenstrup3

Abstract
Ductal and lobular carcinoma in situ (CIS) accounted for 62,280 (24.5%) of all new breast cancer diagnoses in 2009. BRCA1/2 mutations confer an extremely high risk of breast cancer, and management guidelines for BRCA1/2 mutation carriers advise close follow-up, intensive screening, and consideration of prophylactic surgery to lower this risk. The limited relevant previous data are not definitive in establishing the prevalence of BRCA1/2 mutations in breast CIS patients, creating uncertainty as to whether referral for cancer risk assessment and genetic testing is appropriate for this group. Therefore, we conducted a cross-sectional analysis of the Myriad Genetics BRCA1/2 database to determine the prevalence of these mutations in breast CIS patients. All statistical tests were 2-sided, and confidence intervals (CI) are reported at the 95% level ($\alpha = 0.05$). The source population was 64,717 consecutive women who were not Ashkenazi Jewish, underwent BRCA1/2 testing, and provided a personal and family history of invasive breast and ovarian cancer; 7,295 (11.3%) reported a diagnosis of CIS (ductal or lobular) and had an overall 5.9% prevalence of mutated BRCA1/2 (mBRCA). Subgrouped by history (personal or family) of invasive breast and/or ovarian cancer, these CIS patients had the following prevalences of mBRCA: (1) no personal or family history, 2.3%; (2) personal history, 5.2%; (3) family history, 5%; and (4) personal and family history, 10.3%. mBRCA risk was significantly higher in women with early-onset (<50 years old) CIS than with late-onset ($\geq$50 years old) CIS (odds ratio (OR) = 1.5; 95% CI = 1.1–2.1). Disease onset at less than 40 years age was associated with an even higher mBRCA risk (OR = 1.8; 95% CI = 1.3–2.3). By far the largest analysis of BRCA1/2 mutation prevalence in non-Ashkenazi Jewish breast CIS patients, this study shows that early-onset CIS is associated with mBRCA1/2 in patients referred for genetic testing. When a family history of breast and/or ovarian cancer are also present, testing women with early-onset CIS may increase both the likelihood of detecting BRCA1/2 mutations and opportunities for carriers to consider additional cancer prevention strategies. Cancer Prev Res; 3(12); 1579–85. ©2010 AACR.

Introduction
Carcinoma in situ (CIS) of the breast is an increasingly common diagnosis in U.S. women. Between 1980 and 2001, age-adjusted rates of ductal CIS (DCIS) and lobular CIS (LCIS) increased 7.2-fold and 2.6-fold, respectively (1). CIS accounted for 62,280 (24.5%) of all new breast cancer diagnoses in 2009 (2). Although knowing that a newly diagnosed CIS patient has a BRCA1/2 mutation does not have an immediate impact at the current time on the surgical or oncologic management of the CIS, therapies that target cells with DNA break-repair deficiencies, the characteristic phenotype of mutated BRCA1/2 cells, are in development and may one day alter the current treatment paradigm. The identification of a BRCA1/2 mutation, however, has important implications for carriers in general. Deletorious mutations in the BRCA1/2 genes are the principal cause of hereditary breast–ovarian cancer (3, 4). The lifetime risk of breast cancer in BRCA1/2 mutation carriers has been reported to be as high as 87% (5, 6). Elevated risks also occur for ovarian cancer (as high as 44% in mutation carriers by age 70) and contralateral breast cancer (5, 7–9). Bilateral prophylactic mastectomy and salpingo-oophorectomy have been shown to reduce the risk of breast and ovarian cancer in BRCA1/2 mutation carriers (10, 11). With the knowledge of a BRCA1/2 mutation and the high cancer risks associated with being a mutation carrier, women may elect intensive cancer screening, chemoprevention, and/or prophylactic removal of the ovaries or breasts even if they have never personally been affected by cancer.

It is unclear whether women with CIS, like their counterparts with invasive breast cancer, warrant genetic risk...
assessment and genetic testing to guide future health decisions. CIS has long been suspected to be associated with the hereditary breast-ovarian syndrome, but early data did not support this notion (12). A 1996 review of 36 BRCA1-positive families identified only 4 occurrences of DCIS compared with over 200 invasive breast cancers (13). Early studies from the Breast Cancer Linkage Consortium confirmed a lower prevalence of DCIS (14) and a lower risk of DCIS associated with invasive breast cancer (15) in BRCA1/2 mutation carriers. Subsequent analyses, however, have supported the existence of a CIS-associated premalignant pathway in mutation carriers (16–18). Among women referred for genetic risk assessment with a BRCA-Pro mutation probability greater than 10%, DCIS prevalence estimates were comparable in BRCA1/2 mutation carriers versus mutation negative women (17).

Individuals are increasingly choosing predictive genetic testing as a means of quantifying future cancer risks and informing decisions regarding breast and ovarian cancer screening, chemoprevention, and surgical risk reduction. Among the first 10,000 women undergoing genetic testing through Myriad, 13% diagnosed with CIS before the age of 50 had a deleterious (disease-causing) BRCA1/2 mutation (19). In recent years, improved mutation detection coupled with an expanded testing cohort has allowed refinement of these estimates. Nevertheless, the relatively small previous studies of the relationship between BRCA1/2 mutations and breast DCIS (16–18) are not definitive. Here, we report the largest study of the prevalence of deleterious BRCA1/2 mutations in a population of women reporting CIS (ductal or lobular) derived from a large sample of consecutive individuals referred for comprehensive BRCA1/2 genetic testing using DNA sequencing and rearrangement testing technology.

Methods

Database

The data source for this cross-sectional study has been the subject of a number of previous reports (19–21). Established in 1996 and supported by Myriad Genetics, the Myriad BRCA1/2 clinical database organizes the personal and family cancer history and mutation data collected on all individuals tested for BRCA1 and BRCA2 mutations. The database includes all individuals who have undergone testing, including those receiving (1) full-sequence DNA analysis of the BRCA1/2 genes; (2) site-specific DNA testing for persons with a known familial mutation; (3) founder panel testing at 3 sites for 2 highly prevalent mutations in BRCA1 (187delAG and 5385insC) and 1 in BRCA2 (6174delT) found primarily in the Ashkenazi Jewish (AJ) population. This database has been used in part to generate BRCA1/2 mutation and large genomic rearrangement prevalence estimates accessible by the public for clinical and research purposes (22).

Study population

A consecutive set of individuals referred to Myriad for genetic testing from 2006 to 2008 were considered for this study. Subjects included in the study underwent clinical full-sequence BRCA1/2 analysis, were female, and completed the personal and family history sections of the test requisition form (TRF). AJ women were excluded from this analysis because procedures for testing them are substantially different. Most AJ women undergo initial founder mutation screening/testing, and, if positive, do not receive full-sequence analysis. Unique testing procedures have been developed through our laboratory (i.e., the Multisite 3 BRACAnalysis test) for AJ individuals because of the high rate of 3 founder mutations in BRCA1/2 in carriers among this population.

Personal and family history

Personal and family history data were collected from a TRF included in each testing kit. TRF data are self- and or provider-reported and are unconfirmed. It is important to note that participants who report invasive cancer but no history of CIS may include individuals with concurrent CIS at the time of invasive cancer diagnosis who self-classify by the more severe of the 2 categories (i.e., invasive cancer concurrent with CIS is reported as invasive cancer). For this study, CIS includes both DCIS and LCIS of the breast. To place the prevalence of BRCA1/2 mutations associated with CIS in a clinically relevant context, we divided the study population of self-reported breast CIS patients into the 4 following subgroups: (1) no personal or family history of invasive breast and/or ovarian cancer; (2) any personal history of invasive breast and/or ovarian cancer; (3) any family history (first and/or second degree relatives only) of invasive breast and/or ovarian cancer; and (4) a personal and family history of invasive breast and/or ovarian cancer.

Mutation detection

Full-sequence DNA analysis of BRCA1 and BRCA2 and break-point analysis for 5 common large genomic rearrangements in BRCA1 (exon13del3835bp, exon13ins6kb, exon14–20del26kb, exon22del510bp, and exon8–9del7.1kb) were performed. Technical aspects of these analyses have been previously described in detail (20, 23, 24). In a subset of severe risk women negative by full-sequence DNA analysis and rearrangement testing, additional testing for several rare BRCA1 and BRCA2 large gene deletions and rearrangements (BART) using quantitative multiplex PCR was performed (25). This assay design consists of 11 multiplex reactions with an average depth of 12 amplicons, and a control reaction for PCR contamination. Stringent primer design to avoid common sequence variants, interspersions of BRCA1 and BRCA2 amplicons to minimize the potential of contiguous artifacts, optimized chemistries for GC rich regions, and robust analytical software tools provide a sensitive assay that identifies BRCA1 and BRCA2 rearrangements.

Statistical analysis

The age at which subjects were diagnosed with CIS or invasive cancer was treated as a continuous variable. Mean subject age at the time of CIS diagnosis was calculated for each group of interest and compared using a t test within a...
general linear model. The association of early versus late age of CIS diagnosis to \( BRCA1/2 \) mutation status was assessed by the \( \chi^2 \) test and reported as an odds ratio (OR). All confidence intervals are reported at the 95% significance level. All statistical tests are 2-sided (\( \alpha = 0.05 \)). Analyses were performed using Stata statistical software (Stata Corporation).

**Results**

**Study-population characteristics**

During the study period (2006–2008), 64,717 consecutively tested individuals underwent DNA full-sequence analysis of \( BRCA1 \) and \( BRCA2 \), including rearrangement panel testing, were not AJ, and returned a completed TRF to our laboratory, thus meeting the inclusion criteria for this analysis. On the basis of personal and family history information collected from the TRF, 7,295 (11.3%) of the tested women reported a personal history of CIS (any reported CIS). The 4 major subgroups of CIS patients with regard to a personal and/or family history of invasive breast and/or ovarian cancer were as follows (Table 1): (1) no personal or family history (738 of 7,295, 10.1%); (2) personal history (347 of 7,295, 4.8%); (3) family history (4,638 of 7,295, 63.6%); and (4) personal and family history (1,572 of 7,295, 21.5%).

**Prevalence of \( BRCA1/2 \) mutations by cancer-history subgroup**

DNA full-sequence analysis of \( BRCA1/2 \) revealed deleterious mutations in 5.9% (\( n = 428 \)) of all tested subjects (\( n = 7,295 \)) with CIS (any reported CIS). The prevalences of deleterious \( BRCA1/2 \) mutations in the 4 major subgroups (with regard to a personal and/or family history of invasive breast and/or ovarian cancer) were as follows (Table 1): (1) 2.3% in CIS patients with no personal or family history; (2) 5.2% in patients with a personal history; (3) 5% in patients with a family history; and (4) 10.3% in patients with a personal and family history. More than half of these mutations (\( n = 9 \)) in CIS-alone group (no invasive cancer history) were in women ages 40 years and younger. Mutation prevalence in individuals with CIS and no personal history of invasive cancer (CIS alone + CIS and any family history subgroups) is compared with prevalence in individuals reporting a history of invasive cancer and no personal history of CIS in Table 2, and is stratified by the gene affected. Here, it can be seen that a personal history of CIS (no personal history of CIS; OR = 0.42; 95% CI = 0.37–0.48). The distribution of \( BRCA1/2 \) mutations in CIS (CIS alone + CIS and any family history subgroups) also differs from that of invasive breast cancer (no personal history of CIS), in that \( BRCA2 \) mutations are more prevalent in the former (OR 3.25; 95% CI = 2.43–4.39; Table 2). The prevalence of a \( BRCA1/2 \) variant of uncertain significance was similar in women with CIS alone (41 of 738, 5.6%), CIS and any personal history (18 of 347, 5.2%), CIS and any family history (242 of 4,638, 5.2%), and CIS and a personal and family history (77 of 1,572, 4.9%; \( P = 0.9 \)).

**Early-onset CIS**

\( BRCA1/2 \) carriers are predisposed to develop early-onset (<50 years) invasive breast cancer (\( BRCA1 > BRCA2 \); ref. 5).
Early-onset CIS (<50 years) is also a marker of carrier status (Table 3). Among women in the CIS alone + CIS and any family history subgroups (CIS and any personal history excluded), those with early-onset CIS had a significantly increased risk of a \( BRCA1/2 \) mutation compared with women with late-onset disease (>50 years; OR 1.5; 95% CI = 1.1–2.1). The point estimate of this association was higher in women with very early-onset disease (<40 years versus >40 years of age; OR 1.8; 95% CI = 1.3–2.3).

**Discussion**

With a source population of 64,717 women tested for \( BRCA1/2 \) mutations and a derived population of 7,295 breast CIS (ductal and lobular) patients, this study is the largest one we know of to evaluate \( BRCA1/2 \)-mutation prevalence in breast CIS patients; it demonstrates that CIS is part of the cancer spectrum in \( BRCA1/2 \) carriers, which is consistent with some earlier observations (16–18, 26, 27). Our major findings include an overall 5.9% prevalence of deleterious \( BRCA1/2 \) mutations in CIS patients, an increasing prevalence of these mutations (from 2.3% to 10.3%) based on increasing severity of personal and/or family history of invasive breast and/or ovarian cancer, and a significant association of these mutations with early-onset CIS.

Claus et al. (16) reported \( BRCA1/2 \) mutation prevalence of 3.3% (12 of 369) in a population-based sample of women with DCIS from the Connecticut Tumor Registry. Carrier status was significantly associated with a personal history of ovarian cancer or early-onset breast cancer and with a family history of breast cancer in a first-degree relative, particularly when the relative was diagnosed at less than 50 years of age (OR = 10.6; 95% CI = 3.0–37.0). Despite the similarities between this study and our study and a partial overlap of study populations, several important differences should be highlighted as they would be anticipated to differentially impact the magnitude of the \( BRCA1/2 \) prevalence estimates reported in each study. Most important, the current study’s exclusion of AJ individuals, whose frequency of \( BRCA1/2 \) mutations is higher than average because of the presence of 3 well-described founder mutations in the AJ population (17), would be expected to result in comparatively lower prevalence estimates than the analysis does not include the 1,919 patients with CIS and a personal history of invasive cancer or the 17,107 with neither CIS or a personal history of invasive cancer.

<table>
<thead>
<tr>
<th>Personal history</th>
<th>Total subjects (N)</th>
<th>Mutation carriers</th>
<th>OR (95% CI)</th>
<th>BRCA1, n (%)</th>
<th>BRCA2, n (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS without a personal history of invasive cancer</td>
<td>5,376 (11.8)</td>
<td>248 (4.6)</td>
<td>–</td>
<td>69 (27.8)</td>
<td>179 (72.2)</td>
<td>–</td>
</tr>
<tr>
<td>Personal history of invasive cancer without a history of CIS</td>
<td>40,315 (88.2)</td>
<td>4,152e (10.3)</td>
<td>0.42 (0.37–0.48)</td>
<td>2,301 (55.6)</td>
<td>1,836 (44.4)</td>
<td>3.25 (2.43–4.39)</td>
</tr>
</tbody>
</table>

The analysis does not include the 1,919 patients with CIS and a personal history of invasive cancer or the 17,107 with neither CIS or a personal history of invasive cancer.

<table>
<thead>
<tr>
<th>Age of carcinoma in situ diagnosis</th>
<th>Subjects/total CIS (%)</th>
<th>( BRCA1/2 ) mutation prevalence, n (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>3,704/5,376 (68.9)</td>
<td>191 (5.2)</td>
<td>(50 vs 50) 1.5 (1.1–2.1)</td>
</tr>
<tr>
<td>&lt;40</td>
<td>1,107/5,376 (20.6)</td>
<td>76 (6.9)</td>
<td>(40 vs 40) 1.8 (1.3–2.3)</td>
</tr>
</tbody>
</table>

Includes individuals with CIS alone and CIS and any family history of breast or ovarian cancer; excludes individuals with a personal diagnosis of invasive breast or ovarian cancer.
those of Claus et al. The inability to confirm histology on all tested patients and thus the inability to exclude women with LCIS, a preinvasive pathology that has not been associated with BRCA1/2 mutations, or other non-DCIS histologies would also be expected to lower prevalence estimates in our sample subgroups. On the basis of historical data (1), however, we believe that LCIS likely accounted for less than 10% of our cases. Conversely, prevalence estimates in the current study may be positively impacted (i.e., higher) relative to Claus et al. because our BRCA1/2 testing occurred several years later than that of Claus et al., affording the current study the benefits of improved mutation detection techniques and additional testing experience on the part of the scientific community and Myriad.

Other recent studies also offer insight into the role of BRCA1/2 in CIS of the breast. Hwang et al. (17) retrospectively examined breast cancer and risk factor–related data in a cohort of women self- or physician-referred for genetic testing, identifying DCIS more commonly among mutation carriers (37%) compared with noncarriers (34%). In multivariate modeling, mutation carriers had a greater hazard for DCIS (hazard ratio = 1.45; 95% CI = 0.98–2.14) and invasive cancer (hazard ratio = 1.60; 95% CI = 1.12–2.30) compared with noncarriers. Smith et al. (18) examined the relationship of DCIS to BRCA1/2 mutations through 3 nonoverlapping groups ascertained through a large urban-based cancer center. They found that the prevalence of AJ BRCA1/2 founder mutation was 0% in a prospectively ascertained surgical population with newly diagnosed DCIS and 4.8% in an ongoing follow-up population of AJ women with a history of DCIS. Prevalence in a mixed AJ/non-AJ sample from a cancer risk-assessment clinic–based population of DCIS patients was 12.7%, which was lower than that in all (14%) or early-onset (17%) invasive breast cancer patients. Though observational, our results provide additional clinically practical data on a diverse group of U.S. women diagnosed with CIS during their lifetime. In a heterogeneous clinical referral population tested for BRCA1/2 mutations, we demonstrate the contribution of various components of personal and family history of in situ and invasive cancer to the prevalence of BRCA1/2 mutations, and show that early-onset CIS (age of onset <50 years) in a population unsellected for family history is significantly associated (OR = 1.5; 95% CI = 1.1–2.1) with the presence of a deleterious BRCA1/2 mutation by full-sequence DNA testing (the mutation OR for women less than 40 years old was a significant 1.8; 95% CI = 1.3–2.3). Both of these clinic-based studies included AJ women, who were excluded from our study; an added strength of theirs, however, was the ability to identify and limit the analyses to DCIS. Although our data are not clinic-based and comprise DCIS and LCIS, they are strengthened by the large size of our population of 7,295 CIS patients, which compares with much smaller sample sizes in the Hwang et al. (n = 398) and Smith et al. (n = 199) studies.

For women who are diagnosed with CIS, particularly those with additional personal and family history of breast and/or ovarian cancer, the implications of these results are many, as researchers continue to discover better means to lower cancer risks in mutation carriers. At the present time there is little data to support the notion that CIS in BRCA1/2 carriers should be treated differently than CIS occurring in a nonmutation carrier. However, the knowledge of a BRCA1/2 mutation is likely to significantly change the assessment of a CIS patient’s risks for future cancers and the cancer prevention and risk reduction recommendations that would be considered. Women made aware of a germ-line BRCA1/2 mutation may consider several screening and prophylaxis options to lower their breast and/or ovarian cancer risk, including the use of magnetic resonance imaging to screen for breast cancer, surgical prophylaxis options such as mastectomy or salpingo-oophorectomy, or chemoprevention (e.g., tamoxifen or a clinical trial; refs. 10, 11, 28–31). Carriers also may wish to provide their mutation status to close family members and thus provide them the opportunity to pursue single-site testing for the familial mutation and to consider possible cancer prevention measures.

Although representative of BRCA1/2 testing results for a vast number of women, our data are nonetheless difficult to compare to previous studies, and should not be used to draw conclusions about mutation prevalence in the general population because of the highly select nature of our subject ascertainment. Because the TRF does not explicitly collect information on CIS subtype (DCIS/LCIS), we are unable to distinguish the fraction of CIS in our sample that is represented by LCIS or the mutation prevalence in either of these CIS subgroups. In the general population, LCIS represents roughly 10% of incident CIS (1) but, unlike DCIS, has not been associated with germ-line BRCA1/2 mutations. Nonetheless, whether providers are more or less likely to refer for BRCA1/2 genetic testing in women with LCIS versus DCIS is unknown. Variable completeness of DNA testing performed across studies (e.g., AJ panel versus full DNA sequence ± genomic rearrangement testing) and the limits imposed by self-reported personal and family history information gathered from the TRF are additional important limitations to consider. How and whether a history of CIS is reported in women referred for genetic testing may also influence the interpretation of these data and limit our conclusions. CIS represents roughly one fourth of all newly diagnosed breast cancers, yet has a prevalence of only 11% in our sample. It is likely that some patients and providers consider CIS and invasive breast cancer as interchangeable and therefore do not make a distinction between them on the TRF. Equally, a later diagnosis of invasive breast cancer may trump an earlier CIS diagnosis that will, subsequently, remain unreported. If true mutation prevalence in CIS is overall lower than mutation prevalence in invasive breast cancer, but higher in certain high-risk subgroups (e.g., CIS < 50), the first misclassification could simultaneously dilute mutation prevalence estimates in women with invasive breast cancer and lower prevalence estimates in CIS by removing the subgroup of CIS more likely to carry mutations. CIS
underreporting may also occur in women with a history of CIS and a concurrent diagnosis of invasive cancer, because invasive breast cancer history may be felt to better define pretesting risk than CIS. Individuals reporting a history of CIS constitute a sizeable fraction (11.3%) of the population of women undergoing commercial BRCA1/2 testing at the present time. As would be expected, the likelihood of a woman with CIS carrying a BRCA1/2 mutation increases not only with a diagnosis of invasive breast cancer but also as family history strengthens and age of CIS diagnosis decreases, permitting counseling and testing resources to be targeted more effectively. Few women had a history of CIS alone (no other personal or family history of invasive cancer or CIS), suggesting that genetic testing referral for CIS alone is rare.

CIS may be more strongly associated with BRCA2 mutations (3, 4). One possible rationale for this finding may relate to tumor biology, as BRCA2-positive women are more likely to have estrogen receptor (ER)-positive tumors (32) and DCIS is most often ER-positive (33). Women reporting CIS preceding a diagnosis of invasive breast cancer represented a small portion of our sample, and we did not find a difference in the mean reported time interval between CIS and invasive cancer in mutation carriers versus noncarriers. Because CIS and invasive breast cancer diagnosis histories were collected independent of mutation status, this represents an interesting finding, but one that should not be overinterpreted, as these data cannot account for differential screening biases that may have existed in these 2 groups, affecting both the timing of each diagnosis and the duration of the time interval in between them. Finally, the inclusion of LCIS in our sample, the natural history of which is not definitively linked to invasive cancer, may also bias our findings.

Ultimately, decisions on referral for genetic testing remain most difficult in cases of late-onset disease (CIS or invasive breast cancer) and minimal family history. This referral is far more straightforward in the case of women with early-onset CIS (diagnosed before age 50), particularly when a family history of breast and/or ovarian cancer is also present, who have an increased likelihood of mutation detection. Posttreatment survival estimates and quality-of-life measures in most CIS patients are far superior to those of invasive breast cancer patients (34, 35). Therefore, genetic testing in the setting of CIS and other personal or familial risk factors for hereditary breast–ovarian cancer may be useful in providing at-risk women the ability to better protect themselves from cancer by quantifying their personal invasive cancer risk. Furthermore, many of these women will use personal genetic information to inform family members of possible inherited risks that may be modified to prevent cancer.

Disclosure of Potential Conflicts of Interest

J.E. Reid and R.J. Wenstrup are employees of Myriad Genetic Laboratories, Inc., and have stock options in Myriad Genetic Laboratories, Inc. No other potential conflicts of interest were declared.

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