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Prevalence of *BRCA1* and *BRCA2* mutations in women with carcinoma *in situ* of the breast referred for genetic testing

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Abstract

Background—Carcinoma *in situ* (CIS) of the breast will account for 62,280 (24.5%) of new breast cancer diagnoses in 2009. Management guidelines for *BRCA1/2* mutation carriers advise close follow-up, intensive screening, and consideration of prophylactic surgeries to lower cancer risk. The prevalence of *BRCA1/2* mutations in women with a history of CIS using comprehensive DNA sequencing and rearrangement testing has not been definitively documented.

Methods—The prevalence of mutations in non-Ashkenazi Jewish women with CIS was assessed by way of a cross-sectional analysis of the Myriad Genetic Laboratories, Inc. *BRCA1/2* database. Women reporting any diagnosis of CIS were included. All statistical tests are two-sided, and confidence intervals are reported at the 95% level (α =0.05).

Results—Among the test population (N=64717), 11.3%(n=7295) reported a history of CIS (*any reported CIS*). For women without personal history of invasive cancer (*CIS alone+CIS and any family history* subgroups), those with early-onset CIS had a significantly increased risk of a *BRCA1/2* mutation compared to women with late-onset disease (≥50 years)(OR 1.5, 95% CI 1.1–2.1). Among women reporting only a history of CIS and no personal or family history (*CIS alone*), mutation prevalence was 2.3% (17/738).

Conclusions—In patients referred for genetic testing, early-onset CIS is associated with *BRCA1/2*. When a family history of breast and/or ovarian cancer are also present, testing women with early-onset CIS may increase the likelihood of *BRCA1/2* mutation detection, and the opportunity for carriers to consider additional cancer prevention strategies.

Keywords

BRCA1; BRCA2; carcinoma in situ

Introduction

Carcinoma *in situ* (CIS) of the breast is an increasingly common diagnosis in American women. Between 1980 and 2001, age-adjusted rates of ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS) increased 7.2-fold and 2.6 fold, respectively (1). CIS will account for 62,280 or 24.5% of new breast cancer diagnoses in 2009 (2).

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CIS has long been suspected to be associated with the hereditary breast-ovarian syndrome, but early on data supporting this notion were lacking (3). A 1996 review of 36 *BRCA1*-positive families identified only 4 occurrences of DCIS compared to over 200 invasive breast cancers (4). Early studies from the Breast Cancer Linkage Consortium (BCLC) confirmed a lower prevalence of DCIS (5) and a lower risk of DCIS associated with invasive breast cancer (6) in *BRCA1/2* mutation carriers. Subsequent analyses, however, have supported the existence of a CIS-associated pre-malignant pathway in mutation carriers (7–9). Among women referred for genetic risk assessment with a BRCAPRO mutation probability > 10%, DCIS prevalence estimates were comparable in *BRCA1/2* mutation carriers vs mutation negative women (8). Increased risks of DCIS in mutation carriers (7) and elevated mutation prevalence in women with DCIS presenting to a hereditary risk assessment clinic (12.7%) (9) have also been reported. Pathologic studies of breast tissue from mutation carriers undergoing mastectomy have additionally supported a high prevalence of pre-malignant lesions including DCIS and LCIS in mutation carriers (10–12) as well as high-risk mutation-negative women (11,13).

The identification of a *BRCA1/2* mutation has important implications for mutation carriers. Deleterious mutations in the *BRCA1/2* genes are the principal cause of hereditary breast-ovarian cancer (HBOC)(14,15). The lifetime risk of breast cancer in mutation carriers has been reported to be as high as 87% (16,17). The risks of ovarian cancer (as high as 44% in mutation carriers by age 70) and contra-lateral breast cancer are also elevated (16,18–20).

Individuals are increasingly choosing predictive genetic testing (PGT) 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% of women diagnosed with CIS before the age of 50 had a deleterious (disease-causing) *BRCA1/2* mutation (21). In recent years, improved mutation detection coupled with an expanded testing cohort has allowed better refinement of these estimates. Here, we report the prevalence of deleterious *BRCA1/2* mutations in women reporting CIS 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 (21–23). Established in 1996, 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, and is supported by Myriad Genetic Laboratories (Myriad). 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 three sites for two highly prevalent mutations in *BRCA1* (187delAG and 5385insC) and one in *BRCA2* (6174delT) found primarily in the Ashkenazi Jewish 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 (24).

Study Population

A consecutive set of individuals referred to Myriad for genetic testing during 2006 – 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 cancer

history sections of the test requisition form (TRF). Ashkenazi Jews were excluded from this analysis because testing procedures are substantially different in this group—most Ashkenazi women undergo initial founder mutation screening/testing, and, if positive, do not receive full-sequence analysis. 64,717 consecutively tested individuals met the inclusion criteria for this analysis.

Personal and family history

Personal and family history data were collected from a test requisition form (TRF) included in each testing kit. TRF data are self- and or provider-reported and are unconfirmed. For this study, CIS includes both ductal carcinoma *in situ* and lobular carcinoma *in situ* of the breast. To place the prevalence of *BRCA1/2* mutations associated with CIS in a clinically relevant context, CIS is reported in several formats (see Table I): *CIS alone* includes women with CIS and no other personal or family history of invasive breast or ovarian cancer; *CIS and any personal history* includes women reporting a personal history of CIS and a personal history of either invasive breast cancer, ovarian cancer, or both invasive breast cancer and ovarian cancer; *CIS and any family history* includes women with a personal history of CIS and a family history (1^{st} and/or 2^{nd} degree relatives only) of invasive breast cancer, ovarian cancer or both breast and ovarian cancer; *CIS and personal history and family history* includes women with CIS, a personal history of invasive breast and/or ovarian cancer and a family history of invasive breast and/or ovarian cancer; *Any reported CIS* contains the total of individuals from these 4 mutually exclusive groups.

Mutation detection

Full-sequence DNA analysis of *BRCA1* and *BRCA2* and break-point analysis for five 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 (22,25,26). 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 (27). 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, interspersion 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 (GLM). The association of early vs late age of CIS diagnosis to *BRCA1/2* mutation status was assessed by the χ^2 test and reported as an odds ratio (OR). All confidence intervals are reported at the 95% significance level. All statistical tests are two-sided ($\alpha = 0.05$). Analyses were performed using Stata statistical software (Stata Corporation, College Station, TX).

Results

During the study period, 64,717 individuals underwent DNA full-sequence analysis of *BRCA1* and *BRCA2*, including rearrangement panel testing, and returned a completed TRF to our laboratory.

Prevalence of carcinoma *in situ* and *BRCA1/2* mutations

We examined personal and family history information collected from the TRF. 11.3% (n=7295) of women reported a personal history of CIS (*any reported CIS*). Nearly two-thirds (63.6%) of these individuals reported a personal history of CIS concurrent with a family history of invasive breast, ovarian, or both breast and ovarian cancer. Mean age in this *CIS and any family history* subgroup was 47.3 years [SD 9.2 years, Median 46 years, range 18–86)]. A fraction of women with CIS (10.1%, n=738) reported no personal or family history of invasive cancer. The mean age of CIS diagnosis of this group (*CIS alone*) was 41.8 years [SD 8.1 years, Median 41 years, range 18–76) ($p<0.001$).

DNA full-sequence analysis of *BRCA1/2* revealed deleterious mutations in 5.9% (428/7295) of all tested subjects with CIS (*any reported CIS*). In the *CIS alone* subgroup (no personal or family history), (17/738, 2.3%) were detected. More than half of these mutations (n=9) were seen in women 40 years of age and younger. The prevalence of CIS stratified by personal history, family history, and *BRCA1/2* mutation status is presented in Table 1. Mutation prevalence in individuals with CIS and no personal history of invasive cancer (*CIS alone +CIS and any family history* subgroups) is compared to prevalence in individuals reporting a history of invasive cancer and no personal history of CIS in Table 2, and is stratified by gene affected. Here, it can be seen that a personal history of CIS but no invasive cancer (*CIS alone+CIS and any family history* subgroups) is a less powerful predictor of carrying a *BRCA1/2* mutation than a personal history of invasive cancer (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)] (see Table 2). The prevalence of a variant of uncertain significance was similar in women with *CIS alone* [41/738 5.6%], *CIS and any personal history* [18/347 (5.2%)], *CIS and any family history* [242/4638, 5.2%)], and *CIS and personal history and family history* [77/1572, 4.9%) ($p=0.9$).

Early onset carcinoma *in situ*

BRCA1/2 carriers are predisposed to develop early-onset (< 50 years) invasive breast cancer (*BRCA1>BRCA2*) (16). 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 to 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 vs ≥40 years of age)(OR 1.8, 95% CI 1.3–2.3).

Carcinoma *in situ* preceding invasive breast cancer

It is unknown if invasive breast cancer is preceded by clinically detectable carcinoma *in situ*, or which physiologic or environmental factors might predispose to and/or accelerate the transition from CIS to invasive cancer. In our sample, a small number of women (n = 487) reported a diagnosis of CIS followed by a later diagnosis of invasive breast cancer (subset of women from the *CIS and any personal history* group). Forty-one (8.4%) were found to carry a *BRCA1/2* mutation (all were tested for *BRCA1/2* after the diagnosis of invasive breast cancer). There was no difference in the interval of time between CIS and invasive breast cancer in carriers (mean 8.4 years, SD 5.8 years) versus non-carriers (mean 7.9 years, SD 6.6 years)($p=0.6$).

Discussion

We demonstrate that CIS is part of the cancer spectrum found in *BRCA1/2* carriers, supporting earlier observations (7–9). Claus et al (7) reported *BRCA1/2* mutation prevalence of 3.3% (12/369) 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 a family history of breast cancer in a first-degree relative, particularly when early-onset (OR 10.6, CI 3.0–37.0). In the present study, we report variable carrier status estimates from a large commercial database ranging from 2.3% (*CIS alone*) to 5.0% (*CIS and any family history*) to 10.3% (*CIS and personal history and family history*). Despite the similarities in these two studies and partial population overlap, 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 importantly, the exclusion of Ashkenazi Jewish individuals from the current study, among whom *BRCA1/2* mutations are more frequent due to the presence of three well-described founder mutations in the Ashkenazi population (8), would be expected to result in comparatively lower prevalence estimates than those of Claus et al. The inability to confirm histology on all tested patients, allowing the exclusion of women with lobular carcinoma *in situ*, a pre-invasive pathology that has not been associated with *BRCA1/2* mutations, or other non-DCIS histologies, would also be expected to result in lower prevalence estimates in our sample subgroups. Conversely, prevalence estimates in the current study may be positively impacted (i.e. higher) relative to Claus because *BRCA1/2* testing here was performed several years subsequent to 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 additional insight into the role of *BRCA1/2* in CIS of the breast. In Hwang et al (8), breast cancer and risk factor related data on a cohort of women self- or physician-referred for genetic testing were examined retrospectively, and DCIS was identified more commonly among mutation carriers compared to non-carriers (37% vs 34%). In multivariate modeling, mutation carriers were found to have greater hazard for DCIS [1.45 (0.98–2.14)] and invasive cancer [1.60 (1.12–2.30)] compared to non-carriers. Smith et al (9) examined the relationship of DCIS to *BRCA1/2* mutations through three non-overlapping groups ascertained through a large urban-based cancer center. Ashkenazi Jewish (AJ) *BRCA1/2* founder mutation prevalence in an incident (0%) and prevalent (4.8%) population of AJ women with CIS was reported. Prevalence in a mixed AJ/non-AJ sample from a cancer risk assessment clinic-based population (12.7%) was also reported to be lower than that in all (14%) and early-onset disease (17%) in women with invasive breast cancer. Though observational, our results provide additional clinically practical data on the diverse segment of US women who have been diagnosed with carcinoma *in situ* 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 unselected for family history is significantly associated (OR 1.5, 95% CI 1.1–2.1) with the presence of a deleterious mutation by full-sequence DNA testing.

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 for their CIS than CIS occurring in a non-mutation carrier. While all patients with CIS are at increased risk for another breast cancer event, those with a *BRCA1/2*

mutation have a very high lifetime risk of breast cancer and also have a significantly elevated risk of ovarian cancer (16–20). Thus, the knowledge of a *BRCA1/2* mutation is likely to significantly change the assessment of their 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 (MRI) to screen for breast cancer, surgical prophylaxis options such as mastectomy or salpingo-oophorectomy, or chemoprevention (e.g. tamoxifen or a clinical trial)(28–33). Carriers may also wish to inform close family members of their mutation status, allowing them the option to themselves pursue single-site testing for the familial mutation and to consider possible cancer prevention measures.

While 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 due to the highly select nature of our subject ascertainment. Because the test requisition form (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 nor 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 vs DCIS is unknown. Variable completeness of DNA testing performed across studies (e.g. Ashkenazi panel vs 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 ¼ 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 test requisition form. 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 sub-groups (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 sub-group 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, since invasive breast cancer history may be felt to better define pre-testing 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), and in this subgroup, age of CIS diagnosis was early (42 years). This suggests that genetic testing referral for CIS alone is rare, but that early-onset CIS, like invasive disease, may lower physician and patient thresholds for referral and/or pursuit of testing.

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 (34) and DCIS is most often ER-positive (35). 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 non-carriers. 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 over-interpreted, as these data cannot account for differential screening biases that may have existed in these two 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. However, based on the epidemiology of DCIS and LCIS in the general population, we would expect LCIS to account for < 10% of the sample studied here.

Ultimately, decisions related to referral for genetic testing remain most difficult in those individuals with later onset disease (CIS or invasive breast cancer) and minimal family history. Identifying women with early-onset CIS (women diagnosed with CIS before age 50) for genetic testing, particularly when a family history of breast and/or ovarian cancer is also present, will increase the likelihood of mutation detection. With post-treatment survival estimates and quality of life measures in most CIS patients far superior to those of invasive breast cancer (36,37), genetic testing in the setting of a diagnosis 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 risk of future breast and ovarian cancer. Moreover, many will use personal genetic information to instruct family members of possible inherited risks that may be averted or modified before cancer is diagnosed.

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References

1. Li CI, Daling JR, Malone KE. Age-specific incidence rates of in situ breast carcinomas by histologic type, 1980–2001. Cancer Epidemiol Biomarkers Prev 2005;14(4):1008–11. [PubMed: 15824180]
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59(4):225–49. [PubMed: 19474385]
3. Narod SA, Offit K. Prevention and management of hereditary breast cancer. J Clin Oncol 2005;13:1656–63. [PubMed: 15755973]
4. Sun CC, Lenoir G, Lynch H, Narod SA. In-situ breast cancer and BRCA1. Lancet 1996;348(9024): 408. [PubMed: 8709756]
5. Lakhani SR, Jacquemier J, Sloane JP, et al. Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. J Nat Cancer Inst 1998;90(15):1138–45. [PubMed: 9701363]
6. Breast Cancer Linkage Consortium. Pathology of familial breast cancer: Differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. Lancet 1997;349(9064): 1505–10. [PubMed: 9167459]
7. Claus EB, Petruzzela S, Matloff E, Carter D. Prevalence of BRCA1 and BRCA2 mutations in women diagnosed with ductal carcinoma in situ. JAMA 2005;293(8):964–9. [PubMed: 15728167]
8. Hwang ES, McLennan JL, Moore DH, Crawford BB, Esserman LJ, Ziegler JL. Ductal carcinoma in situ in BRCA mutation carriers. J Clin Oncol 2007;25(6):642–7. [PubMed: 17210933]
9. Smith KL, Adank M, Kauff N, et al. BRCA mutations in women with ductal carcinoma in situ. Clin Cancer Res 2007;13(14):4306–10. [PubMed: 17634561]

10. Kauff ND, Brogi E, Scheuer L, et al. Epithelial lesion in prophylactic mastectomy specimens from women with BRCA mutations. Cancer 2003;97(7):1601–8. [PubMed: 12655515]
11. Hoogerbrugge N, Bult P, de Widt-Levert LM, et al. High prevalence of premalignant lesions in prophylactically removed breasts from women at hereditary risk for breast cancer. J Clin Oncol 2003;21(1):41–5. [PubMed: 12506168]
12. Scheuer L, Kauff N, Robsen M, et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. J Clin Oncol 2003;20:1260–8. [PubMed: 11870168]
13. Adem C, Reynolds C, Soderberg CL, et al. Pathologic characteristics of breast parenchyma in patients with hereditary breast carcinoma, including BRCA2 and BRCA2 mutation carriers. Cancer 2003;97(1):1–11. [PubMed: 12491499]
14. Miki Y, Swensen J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994;266:66–71. [PubMed: 7545954]
15. Wooster R, Bignell G, Lancaster J, et al. Identification of the breast cancer susceptibility gene BRCA2. Nature 1995;378:789–792. [PubMed: 8524414]
16. Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium Lancet 1994;343(8899):692–5.
17. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. New Engl J Med 1997;336(20):1401–8. [PubMed: 9145676]
18. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22(12):2328–35. [PubMed: 15197194]
19. Verhoog LC, Brekelmans CTM, Seynaeve C, et al. Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1. Lancet 1998;351 (9099):316–21. [PubMed: 9652611]
20. Whittemore AS, Gong G, Itnyre J. Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: results from three U.S. population-based case-control studies of ovarian cancer. Amer J Hum Genet 1997;60(3):496–504. [PubMed: 9042908]
21. Frank TS, Deffenbaugh AM, Ried JE, et al. Clinical characteristics of individuals with germline mutations in *BRCA1* and *BRCA2*: Analysis of 10,000 individuals. J Clin Oncol 2002;20(6):1480–90. [PubMed: 11896095]
22. Hall MJ, Ried JE, Burbidge LA, et al. BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer. Cancer 2009;115(10):2222–33. [PubMed: 19241424]
23. Bansal A, Critchfield GC, Frank TS, et al. The predictive value of BRCA1 and BRCA2 mutation testing. Genet Testing 2000;4(1):45–8.
24. [confirmed accessible October 13, 2009]. Internet address: http://www.myriadtests.com/provider/doc/BRCA-Mutation-Prevalence-Percentages.pdf
25. Hendrickson BC, Judkins T, Ward BE, et al. Prevalence of five previously reported and recurrent *BRCA1* genetic rearrangement mutations in 20,000 patients from hereditary breast/ovarian cancer families. Genes Chromosomes Cancer 2005;43(3):309–13. [PubMed: 15846789]
26. Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA 2006;295(12):1379–88. [PubMed: 16551709]
27. Claus EB, Stowe M, Carter D. Family history of breast and ovarian cancer and the risk of breast carcinoma in situ. Breast Cancer Research and Treatment 2003;78:7–15. [PubMed: 12611452]
28. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005;365(9473):1769–78. [PubMed: 15910949]
29. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE study group. J Clin Oncol 2004;22(6): 1055–62. [PubMed: 14981104]
30. Kauff ND, Domchek SM, Friebel T, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. J Clin Oncol 2008;26(8):1331–7. [PubMed: 18268356]

31. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 2004;292(11):1317–25. [PubMed: 15367553]

32. [confirmed accessible April 12, 2010]. http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf

33. [confirmed accessible April 12, 2010]. http://www.nccn.org/professionals/physician_gls/PDF/breast_risk.pdf

34. Allred DC, Bryant J, Land S, et al. Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of intraductal breast cancer: findings of the NSABP Protocol B-24. Breast Cancer Res Treat 2002;77(Suppl 1) Abst S36.

35. Goodwin A, Parker S, Ghersi D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast. Cochrane Database Systematic Review. Cochrane Database Syst Rev 2009;3:CD000563. [PubMed: 19588320]

36. van Gestel YR, Voogd AC, Vingerhoets AJ, et al. A comparison of quality of life, disease impact and risk perception in women with invasive breast cancer and ductal carcinoma in situ. Eur J Cancer 2007;43(3):549–56. [PubMed: 17140788]

37. Fisher ER, Land SR, Fisher B, Mamounas E, Gilarski L, Wolmark N. Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project: twelve-year observations concerning lobular carcinoma in situ. Cancer 2004;100(2):238–44. [PubMed: 14716756]

Table 1

Prevalence of *BRCA1/2* mutations in women reporting carcinoma *In situ* of the breast

Associated personal or family history	**Total subjects n (%)[a]**	***BRCA1/2* mutation prevalence n (%)[b]**
CIS alone (no personal or family history of invasive cancer)	**738 (10.1)**	**17 (2.3)**
CIS *and*		
Any personal history	**347 (4.8)**	**18 (5.2)**
Invasive breast cancer only	315 (4.3)	16 (5.1)
Ovarian cancer only	25 (0.3)	2 (8.0)
Both breast and ovarian cancer	7 (0.1)	0 (0.0)
CIS *and*		
Any family history	**4638 (63.6)**	**231 (5.0)**
Invasive breast cancer only	3536 (48.5)	154 (4.4)
Ovarian cancer only	234 (3.2)	10 (4.3)
Both breast and ovarian cancer	868 (11.9)	67 (7.7)
CIS *and* personal history *and* family history	**1572 (21.5)**	**162 (10.3)**
Any reported CIS	**7295 (100)**	**428 (5.9)**

[a] Column percent

[b] Row percent

Table 2

BRCA1/2 mutation prevalence in subjects with CIS and no personal history of invasive cancer (*CIS alone + CIS and any family history*) versus subjects with a history of invasive cancer but no personal history of CIS[a]

Personal history	Total Subjects (N)	Mutation Carriers (n)				
		Total N (%)[b]	OR [95% CI]	*BRCA1* N (%)[c]	*BRCA2* N (%)[c]	OR [95% CI]
CIS without a personal history of invasive cancer[e]	5376 (11.8)	248 (4.6)	--	69 (27.8)	179 (72.2)	--
Personal history of invasive cancer without a history of CIS[f]	40315 (88.2)	4152[d] (10.3)	0.42 [0.37–0.48]	2301 (55.6)	1836 (44.4)	3.25 [2.43–4.39]

Abbreviations: Carcinoma in situ (CIS), odds ratio (OR), 95% confidence interval (95% CI)

[a] The analysis does not include the 1919 patients with CIS and a personal history of invasive cancer or the 17107 with neither CIS or a personal history of invasive cancer

[b] Row percent of total subjects.

[c] Row percent of total mutation carriers

[d] 15 individuals with mutations in BOTH *BRCA1* and *BRCA2* are not counted in either individual gene column for appropriate comparison. Denominator used for percentage computation is 4137

[e] Subjects in this row have no personal history of CIS but may have a family history of cancer. Thus, individuals from *CIS alone* and *CIS and any family history* subgroups are included.

[f] Includes subjects reporting a history of invasive cancer during the study period but no history of CIS.

Table 3

BRCA1/2 mutation prevalence by age of CIS diagnosis (*CIS alone + CIS and any family history*) in women with no history of invasive breast or ovarian cancer[a]

Age of carcinoma *In situ* diagnosis	Subjects n/total CIS (%)	*BRCA1/2* mutation prevalence n (%)	Odds Ratio (95% CI)
CIS < 50	3704/5376 (68.9)	191 (5.2)	*(< 50 vs ≥ 50)* **1.5 (1.1–2.1)**
CIS < 40	1107/5376 (20.6)	76 (6.9)	*(< 40 vs ≥ 40)* **1.8 (1.3–2.3)**

Abbreviations: CIS, carcinoma in situ; CI, confidence interval

[a]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