Hereditary Susceptibility to Breast Cancer: Significance of Age of Onset in Family History and Contribution of BRCA1 and BRCA2

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ABSTRACT (revised): OBJECTIVE: To correlate mutations in BRCA1 and BRCA2 with family history of breast cancer in a first-degree relative for women diagnosed with breast cancer before age 45 who do not have a personal or family history of ovarian cancer.

METHODS: Family history for women with breast cancer diagnosed before age 45 was provided by ordering physicians via a test requisition form designed for this purpose. Gene analysis was performed by dye primer sequencing for the entire coding regions of BRCA1 and BRCA2. Because a personal and family history of ovarian cancer are known to be significantly associated with mutations, women with either were excluded from analysis.

RESULTS: Overall, deleterious mutations in BRCA1 or BRCA2 were identified in 85 of 440 women (19%) with breast cancer under 45. Mutations were identified in 73 of 276 women (26%) with a first degree family history of breast cancer compared to 12 of 164 without (7%) ($P < .0001$). When results were analyzed by the age of diagnosis in first degree relatives, mutations were identified in 56 of 185 women (30%) with at least one first degree relative with breast cancer diagnosed before age 50 compared with 17 of 91 women (19%), where the first degree family history of breast cancer was at or over age 50 ($P = .042$).

CONCLUSION: Among women with breast cancer diagnosed before age 45, a first-degree relative diagnosed with the disease under age 50 is an indicator of a mutation in BRCA1 or BRCA2 even in the absence of a family history of ovarian cancer. Therefore, women diagnosed with early-onset breast cancer should be asked about the age of onset in

any first-degree relative diagnosed with the disease, as well as about any family history of ovarian cancer. Mutations in BRCA2 account for a substantial proportion of hereditary breast cancer. Therefore, studies that are limited to BRCA1 or that do not analyze by age of onset of breast cancer in relatives may underestimate the contribution of mutations in BRCA1 and BRCA2 to women with early onset breast cancer.

BACKGROUND

Approximately 7% of breast cancer arises from inherited genetic mutations [1], the majority of which are in BRCA1 and BRCA2 [2–4]. Inherited mutations in these genes are associated with an elevated risk of breast cancer of 56% to 87% by age 70 [5,6], and 33% to 50% before age 50 [6,7]. In addition, the risk of ovarian cancer by age 70 is 22% [8] to 44% [5,7] in carriers of BRCA1 mutations, and 27% for carriers of mutations in BRCA2 [9].

Although the clinical behavior of breast cancer in BRCA1-BRCA2 mutation carriers appears to be similar to that of non-hereditary breast cancer [10–12], mutations confer an increased risk of a second, contralateral breast cancer [5,10] and a ten-fold increase in the risk of ovarian carcinoma in women who have already been diagnosed with breast cancer [13]. Identifying germline mutations in BRCA1 and BRCA2 therefore has significant implications for the medical management of breast cancer patients as well as their relatives.

It has been shown that a personal or family history of both ovarian and early-onset breast cancer indicates an increased likelihood of an inherited mutation in BRCA1 and BRCA2 [13–

15]. Many studies of site-specific breast cancer families, however, have analyzed only BRCA1 and may not have evaluated the family history according to the age of diagnosis of breast cancer in relatives. We have analyzed the prevalence of mutations in BRCA1 and BRCA2 in women diagnosed with breast cancer before age 45 without a personal or family history of ovarian cancer. We have correlated the results with a history of breast cancer in first-degree relatives (i.e., sister and/or mother) in order to identify women with early-onset breast cancer who should be considered for hereditary breast cancer risk assessment.

OBJECTIVE

To identify which women with breast cancer before age 45 are most likely to carry mutations in BRCA1 and BRCA2.

MATERIALS AND METHODS

Sequence analysis of BRCA1 and BRCA2 was provided as a clinical laboratory service (Myriad Genetic Laboratories, Salt Lake City, UT, USA) to women whose personal or family history indicated the possibility of an inherited mutation in BRCA1 or BRCA2. Exons 2–24 of BRCA1 and exons 2–27 of BRCA2 were amplified using 82 pairs of PCR primers designed to avoid common polymorphisms that might inhibit equal amplification of both alleles. Dye primer

sequencing was performed using fluorescent energy transfer primers (Amersham Life Science Inc, Cleveland, OH, USA), the mutant Taq polymerase F667Y and a thermal stable pyrophosphatase (both from Perkin Elmer, Norwalk, CT, USA). Sequencing reaction products were electrophoresed and detected using a Perkin Elmer Applied Biosystems 377 sequencing apparatus. Analysis of sequence data was performed using software developed by the clinical laboratory. All analyses demonstrating mutations were repeated for verification. For the purposes of this study, individuals with missense mutations of unproven clinical significance were not considered 'positive'.

A personal and family history of cancer and ancestry was provided via a routine laboratory requisition form. Because a personal or family history of ovarian cancer is known to be a significant predictor of a mutation in BRCA1 or BRCA2 [13], women who reported with either were deliberately excluded from this analysis. For the purposes of this study, non-invasive intraductal lesions such as ductal carcinoma-in-situ were not included as 'cancer'.

RESULTS

Overall, 85 of 440 women (19%) with breast cancer diagnosed before age 45 had deleterious mutations, of which 50 occurred in BRCA1 and 35 in BRCA2.

Deleterious mutations in BRCA1 or BRCA2 were identified in 73 of 276 women (26%) with

Table 1
Mutations in BRCA1 and BRCA2 in women with breast cancer diagnosed before age 45 (without a personal or family history of ovarian cancer).

First degree relative with breast cancer < 50 years	First degree relative with breast cancer ≥ 50 years	Total number of women analyzed for BRCA1 and BRCA2	Number of women with mutations in BRCA1	Number of women with mutations in BRCA2	Total number of women with mutations in BRCA1 and BRCA2
no	no	164	3 (1.8%)	9 (5.5%)	12 (7.3%)
no	yes	91	7 (7.7%)	10 (11%)	17 (19%)
yes	no	152	34 (22%)	13 (9%)	47 (31%)
yes	yes	33	6 (18%)	3 (9%)	9 (27%)
	Total	440	50 (11%)	35 (7.9%)	85 (19%)

breast cancer under 45 and a first degree family history of breast cancer at any age, compared to 12 of 164 women (7%) with breast cancer under 45 who reported having no first degree relatives with the disease ($P < .0001$).

When results were analyzed by the age of diagnosis of the first degree relative, mutations were significantly more prevalent in women whose first degree family history included breast cancer before age 50 (56 of 185, 30%) than women whose first degree family history was limited to breast cancer diagnosed at or over age 50 (17 of 91, 19%) ($P = .042$).

The results of this analysis are summarized in Table 1.

CONCLUSIONS

Among women with breast cancer diagnosed before age 45, a first degree relative with breast cancer diagnosed before age 50 is significantly more predictive of a mutation in BRCA1 or BRCA2 than a first degree relative with breast cancer diagnosed at or after age 50.

Mutations in BRCA2 account for a substantial proportion (41 %) of mutations in women with breast cancer diagnosed before age 45, indicating that studies of BRCA1 alone likely underestimate the hereditary contribution to early-onset breast cancer.

Women diagnosed with breast cancer before age 45 with a family history of breast cancer before age 50 in a mother or sister should be evaluated for the possibility of a hereditary cancer syndrome even in the absence of a personal or family history of ovarian cancer.

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