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The prevalence of germline BRCA1 and BRCA2 mutations in young women with breast cancer undergoing breast-conservation therapy

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Abstract

Background: Germline mutations of BRCA1 and BRCA2 increase the risk for breast cancer. Mutation carriers selecting breast-conservation therapy (BCT) for treatment of operable breast cancer experience a higher rate of new primary breast cancers. We sought to determine the frequency of BRCA1/BRCA2 mutations in women who underwent BCT. Genetic testing results were compared with the prior probability of mutations in either gene.

Methods: Eighty-nine patients age 39 or younger entered the study. Genetic testing was performed for BRCA1 and BRCA2 and the BRCAPRO model determined the probability of carrying a mutation.

Results: Eight mutations were discovered (prevalence, 9.0%). Twenty (22%) uncharacterized sequence variants were found. The prior probability of carrying a mutation was 14%. Mutation carriers had a higher prior probability (.49) compared with women with uncharacterized variants (.09) or with normal genes (.11).

Conclusions: BCT and BRCA2 mutations are common (9%) among unselected young breast cancer patients undergoing BCT.

Keywords: Breast cancer; BRCA1; BRCA2; Prior probability; Breast conservation

Breast-conserving therapy (BCT) has become an accepted treatment option for women with early stage breast cancer based on multiple randomized clinical trials showing equivalent survival compared with mastectomy. BRCA1 and BRCA2 were isolated in 1994 and 1995, respectively. Since then, germline mutations in the breast–ovarian susceptibility genes BRCA1 and BRCA2 have identified women at extremely high risk for developing breast cancer. The lifetime risk for breast cancer for mutation carriers is estimated by several studies to be between 50% and 80% [1–3]. The risk of a second primary breast cancer usually is estimated at about 60% as well. Pretreatment determination of BRCA1 or BRCA2 mutations may influence the choice between BCT and mastectomy, and has implications for management of the contralateral unaffected breast.

Approximately 7% of all breast cancers are diagnosed in women before age 40 [3]. However, for women carrying the deleterious mutations in BRCA1 or BRCA2, the average age of breast cancer onset is younger by about a decade compared with the average population [4]. Likewise, disease-associated mutations in either gene are more frequent in women with early onset breast cancer. Previous work established that early onset breast cancer often differs with regards to cause, clinical features, and outcome. Some studies suggest that younger patients, and particularly those patients who have BRCA1 and BRCA2 mutations, have higher local recurrence rates and higher contralateral breast cancer occurrence rates compared with older patients [5].

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Risks for radiation-induced carcinogenesis, ipsilateral breast recurrence, and a new primary breast cancer in the contralateral breast are increased over the general population [6,7].

The increased likelihood of an inherited mutation in this young population and the higher rates of a second primary breast cancer in patients with an inherited mutation suggest a different set of options for initial surgical treatment. The preoperative knowledge of the presence of a germline mutation may have implications for patient management; specifically, BCT followed by radiation may be less attractive for mutation carriers. The patient with a BRCA1 or BRCA2 mutation may wish to have prophylactic surgery on the contralateral breast, and sequence this procedure in the preoperative surgical management.

In this study we measured the prevalence of germline BRCA1 and BRCA2 mutations and compared it with the prior probability of having a germline mutation estimated in a group of women with invasive breast cancer younger than the age of 39 who selected breast conservation.

Methods

A study was designed to determine the outcome of conservatively treated young women with BRCA1 or BRCA2 mutations and to compare the outcome with a similar age group of women who did not harbor a deleterious mutation. We identified 265 potentially eligible women diagnosed with early stage breast cancer younger than 39 years of age who received treatment at the Joint Center for Radiation Therapy in Boston between 1987 and 1996. Eighty-nine patients (34%) agreed to participate. Of the remainder, 17% died before being contacted, 24% opted not to participate, 20% were lost to follow-up evaluation, and 5% were not contacted per the request of the physician.

After Institutional Review Board approval, the patients provided informed consent to undergo genetic testing used for research and not intended for clinical use. The results were kept confidential and were not provided individually to the participating patients. Individuals in the study population who expressed interest in clinical testing were referred to the Cancer Risk and Prevention Clinics at the Dana-Farber Cancer Institute for discussion of risks and benefits of testing. In this study, each patient was assigned a code number along with the blood sample and they were both stripped of patient identifiers to ensure confidentiality.

A questionnaire was developed to explore attitudes about genetic testing and its consequences and the questionnaire was pretested before enrollment. Consenting patients completed an interviewer-administered questionnaire. Pedigree information and a blood sample were collected. Lymphocytes were immortalized by Epstein-Barr virus transformation and stored in liquid nitrogen. The prior probability of harboring a clinically relevant mutation in either BRCA1 or BRCA2 was determined by the BRCAPRO statistical model [8]. This model calculates the probability that an individual carries the deleterious BRCA1 or BRCA2 mutation based on personal and family history of breast and ovarian cancer.

Once all samples were collected, DNA from 89 patients was extracted and plated at appropriate concentrations for subsequent mutation testing. The strategy to detect alterations in BRCA1 and BRCA2 relied on amplification of exons and adjacent intron sequences using polymerase chain reaction followed by conformation-sensitive gel electrophoresis as described by Korrko et al [9]. A mutation was defined as a biochemically relevant change in the genetic sequence, predicted to cause a loss of function in the altered gene, or a previously reported clinically relevant sequence alteration. Relevant changes usually result in truncation of the protein occurring via a frameshift or nonsense codon. An uncharacterized variant (UV) is usually a missense alteration (an amino acid is exchanged for a different amino acid), although the clinical relevance of this change is unknown. Conservative sequence changes (which do not lead to an amino acid substitution) are not reported. Known mutations and UVs are cited in the Breast Cancer Information Core database at the National Institutes of Health (http://research.nhgri.nih.gov/bic/).

Concurrent with the collection phase of the study, patient follow-up data were updated by chart review or by contacting enrolled patients or their physicians to document new contralateral breast cancer, ipsilateral recurrence, distant metastasis, second malignancies, and survival.

Statistical considerations

Descriptive statistics were used in this sample. The BRCAPRO is a statistical model for calculating an individual's probability of carrying a mutation of BRCA1, BRCA2, neither, or both on the basis of the individual's cancer status and the history of breast and ovarian cancer among first- and second-degree relatives. The model uses autosomal-dominant characteristics of the genes, along with prevalence and penetrance, and uses Bayesian updating.

Results

Incidence of genetic factors in young women undergoing breast-conservation therapy

All of the women in this study had undergone BCT for the local treatment of their cancer. Genetic testing results were grouped into negative (no detectable sequence variation), deleterious mutations, or UVs. Eight mutations were identified, 6 in BRCA1 and BRCA2 in BRCA2, representing a 9% carrier frequency overall for both genes. Twenty (22%) UVs were identified. The sensitivity of conformation-sensitive detection is not established and does not detect large-scale gene deletions. Thus, the frequency reported here may underestimate the true frequency of clinically relevant mutations in this cohort of women. The average