ORIGINAL ARTICLE

Effect of Genetic Cancer Risk Assessment on Surgical Decisions at Breast Cancer Diagnosis

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Hypothesis: Breast cancer gene (*BRCA*) mutation status affects patients' surgical decisions when genetic cancer risk assessment is offered at the time of breast cancer diagnosis, prior to definitive treatment.

Patients and Interventions: Outcomes following genetic cancer risk assessment were studied for women newly diagnosed as having breast cancer who were prospectively enrolled in an institutional review board–approved hereditary cancer registry during a 1-year sampling frame. *BRCA* gene analysis was offered to subjects with a calculated mutation probability of 10% or higher. Review of medical records and telephone survey were used to document surgical treatment decisions following genetic cancer risk assessment.

Results: Thirty-seven of 233 women in the registry were enrolled at the time of a breast cancer diagnosis. The interval from diagnosis to genetic cancer risk assessment ranged from 3 to 60 days. The mean calculated probability of a *BRCA* gene mutation was 21% across the cohort. Two women were not tested because of low prior probabilities of mutation detection, and 3 declined owing to intercurrent psychological stressors. Of the remaining 32 patients, no *BRCA* gene mutation was detected in 22 (69%), 3 (9%) were found to carry a variant of uncertain significance, and 7 (22%) had a deleterious mutation. All 7 subjects with a deleterious mutation opted for bilateral mastectomy, whereas 20 of 22 patients with negative test results chose stage-appropriate treatment ($P<.001$).

Conclusions: Genetic cancer risk assessment at the time of breast cancer diagnosis significantly affected women's treatment decisions. Although need and feasibility are demonstrated, the logistics of genetic cancer risk assessment during breast cancer diagnosis prove challenging.

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MOVING QUICKLY from the bench to the bedside, genetic testing for inherited breast cancer susceptibility has become a state-of-the-art standard-of-care option for appropriately selected patients. Mutations in the hereditary breast and ovarian cancer–associated genes, *BRCA1* and *BRCA2*, confer a 56% to 87% lifetime risk of breast cancer and a 15% to 45% risk of ovarian cancer.[1,2] Features such as early-onset breast cancer (age≤40 years), bilateral disease, or family history of breast and/or ovarian cancer are suggestive of genetic predisposition.[3] Quantification of personal and family cancer risk from informative genetic tests may enable women to choose among potential risk reduction interventions such as surgical removal of at-risk tissues (mastectomy and/or salpingo-oophorectomy), chemoprevention, and/or enhanced surveillance, according to their risk tolerance.

See Invited Critique at end of article

Genetic cancer risk assessment (GCRA) is an emerging interdisciplinary subspecialty[3] and optimally includes a team with experienced cancer risk counselors (genetic counselor or advanced-practice nurse in genetics) and a geneticist-oncologist. The GCRA session includes a thorough review of personal and family history as well as a discussion of genetic principles and the potential benefits, risks, and limitations of genetic testing. Analysis of the *BRCA* genes typically takes 3 to 4 weeks following receipt of a blood specimen, and management advice is provided when results are disclosed at a subsequent visit. Several *BRCA* gene mutation probability models (BRCAPRO, Couch, and Myriad) rely on statistical analysis of testing experience, family patterns of cancer, and/or population mutation preva-

lence data to estimate an individual's probability of carrying a mutation and are used to help select candidates for genetic testing.[4-7] The current diagnostic tests for *BRCA1* and *BRCA2* are thought to have a sensitivity of 60% to 90%.[1] A woman with early-onset breast cancer and a strong family history of breast and/or ovarian cancer is likely to have a high pretest mutation probability (eg, >30%) and would therefore be counseled that her test result was probably uninformative if no *BRCA* gene mutation was detected. In addition, the interpretation of test results may be complicated by the not infrequent (10%-15%) finding of variants of uncertain significance (VUS). These are typically missense mutations, often later determined to be benign polymorphisms, rather than the frameshift or truncating mutations that are more easily classified as deleterious and medically significant. Furthermore, there is evidence for other breast cancer predisposition genes. Whereas the finding of a deleterious *BRCA* mutation can be diagnostic of the hereditary circumstance in a given case, a negative result or the finding of a VUS must be interpreted in the context of the clinical setting. Pedigree analysis must be used to form a clinical judgment of the phenotype (high risk for hereditary breast and ovarian cancer or not) to derive the best estimate of empirical new primary breast cancer risk. If the individual has a moderate probability of a mutation, the negative result can be reassuring and indicate likely sporadic disease.

For women with newly diagnosed breast cancer, a myriad of decisions must be made about primary surgical treatment and adjuvant therapy. Breast-conserving therapy (BCT), complete surgical excision of the tumor followed by radiotherapy to the remaining tissue in the affected breast, offers similar survival and local control rates to mastectomy[8-11] and is usually offered in the setting of limited-stage disease if the cosmetic outcome is likely to be acceptable to the patient.[12] In the United States, the utilization rate of BCT for stage I cancer rose from 30% to 68% between 1985 and 1998.[13] There are geographic variations in the use of BCT, with the highest rates in urban areas of the East and West coasts.[14] Limited data exist regarding the results of BCT among women with hereditary breast cancer. Although BCT may be efficacious at 5 years in both hereditary and sporadic breast cancer,[15] *BRCA* mutations are associated with an increased rate of late ipsilateral breast tumor recurrence (22%-48%) at 10 years.[16-18] Most of these cases are thought to represent new primary breast cancers in the previously treated breast. In addition, the lifetime risk for a contralateral second primary breast cancer is between 40% and 60% in *BRCA* mutation carriers, with a risk of 3% to 5% per year, although the higher range of risk may be limited to patients initially diagnosed at a younger age.[19,20] As a result of this greatly increased risk, some *BRCA* mutation carriers may choose the option of mastectomy rather than BCT for initial treatment of the disease as well as risk reduction mastectomy of the contralateral breast in conjunction with initial treatment.[21] There are data supporting the efficacy of risk reduction contralateral mastectomy, and one recent study noted an improved survival rate for selected patients with breast cancer who underwent prophylactic contralateral mastectomy.[22,23] Consequently, GCRA at the time of breast cancer diagnosis may be useful for definitive surgical treatment planning, particularly in women with clinically limited–stage disease. Candidates for this approach include women with a strong family history of breast and/or ovarian cancer and women with early-onset disease (age<50 years regardless of additional family history).

Few data have been published concerning the use of completion mastectomy (ipsilateral and/or contralateral) as a risk reduction choice among *BRCA* mutation carriers with a history of unilateral breast cancer. However, it has been observed that less than 50% of patients who underwent GCRA after completion of breast cancer treatment selected this option.[24-26]

There are several potential logistical and personal challenges to implementing GCRA at the time of a new breast cancer diagnosis: (1) availability of GCRA consultative services; (2) adequate time to complete the GCRA process (initial counseling, informed consent, coordination and determination of insurance coverage for testing, obtaining a blood sample, 2-4 weeks for genotyping, disclosure counseling, and genetic risk–tailored treatment advice); (3) timing of the referral with respect to the current diagnostic and therapeutic treatment sequence (given the obligatory interval between initiation of the genetic test and availability of results); and (4) the challenges of complex decision making and psychological adjustment for patients and their families in the setting of newly diagnosed breast cancer. In addition, the health care professionals involved in the initial diagnosis and treatment of the patient's breast cancer need to be aware of the potential effect of genetic information on their patients' choices to integrate the purpose of the GCRA referral into the initial treatment discussion with the patient. The City of Hope Cancer Genetics Education Program (Duarte, Calif) for health care professionals has created an increased awareness of potential hereditary breast cancer risk and prompted a growing number of GCRA referrals at the time of initial breast cancer diagnosis.[27] To our knowledge, there are no published studies of patients' surgical choices when their genetic status is determined before definitive surgical treatment after a breast cancer diagnosis. The purpose of this study was to determine the effect of *BRCA* gene mutation status on patients' surgical decisions when GCRA is offered at the time of breast cancer diagnosis, prior to definitive treatment.

METHODS

All patients enrolled for GCRA in the City of Hope Cancer Screening & Prevention Program Network are invited to participate in an institutional review board–approved prospective hereditary cancer registry at the time of their initial GCRA consultation. Of these candidates, 98% choose to participate in the registry. Subjects receive prospective follow-up and are periodically contacted for updates of personal and family cancer history as well as for surveillance and surgical decision outcomes. The network is exclusively a referral-consultative practice. All subjects return to their primary caregivers (the referring oncologist or surgeon in most cases) to finalize treatment decisions.

Using the prospective registry during a 1-year sampling frame (May 1, 2000, through April 30, 2001), we ascertained

223 women who underwent GCRA and had a personal or family history of breast cancer. Those with ovarian cancer were not included in this cohort. Subjects with breast cancer who enrolled at the time of diagnosis were categorized as having a newly diagnosed limited-stage (American Joint Committee on Cancer stage I or II[28]) breast cancer and were included in the analysis of outcomes if definitive therapy had not been completed. In every case, GCRA was carried out in a uniform fashion by a team with an experienced cancer risk counselor (advanced-practice nurse in genetics or genetic counselor) and a geneticist-oncologist, with review of each case by a multidisciplinary cancer genetics working group. The GCRA session included a thorough review of personal and family history as well as a discussion of genetic principles and the potential benefits, risks, and limitations of *BRCA* gene analysis. Probabilities of carrying a mutation in the *BRCA1* or *BRCA2* gene were estimated using the Couch model, Myriad model, and BRCAPRO. The model with the highest estimated probability was used for the analyses in this study.[4,5,7]

All subjects were enrolled in the institutional review board–approved registry protocol after providing written informed consent. Genetic testing was offered in cases with a calculated mutation probability of 10% or higher, and the results of genetic testing were disclosed in person at a follow-up visit. The summary visit included a thorough discussion of options for risk management including enhanced surveillance, chemoprevention, and surgical risk reduction, derived from a working group consensus and based in part on National Comprehensive Cancer Network guidelines for patients with hereditary cancer as well as current literature documenting the efficacy of various interventions.[3,22,23,25,29-34] The content of the risk management summary visit did not vary from that offered to individuals who undergo GCRA after the completion of breast cancer treatment and in every case included discussion of new primary risk as distinct from the risk of recurrence.

For patients without a *BRCA* mutation or who carried a VUS, pedigree analysis was used to form a clinical judgment about the phenotype (high risk for hereditary breast and ovarian cancer or not) and informativeness of the test result as well as to derive the best estimate of empirical new primary breast cancer risk. Patients clinically considered to have sporadic disease were counseled that the lifetime risk of a new primary breast cancer ranged from 10% to 30%, the lower limit if adjuvant tamoxifen citrate therapy was planned for an estrogen receptor–positive tumor and the higher limit if the patient was younger than 40 years, consistent with empirical data for contralateral breast cancer among young women.[20] Review of medical records or telephone survey was used to document subjects' decisions about initial surgical treatment of the newly diagnosed breast cancer. The effect of *BRCA* gene mutation status on treatment decisions was measured by χ^2 analysis comparing the women with a deleterious mutation with those who had negative results, according to whether they chose risk reduction surgery.

RESULTS

Of the 223 women who underwent GCRA during a 1-year sampling frame, 143 women had a current or past diagnosis of breast cancer. Thirty-seven women (26%) underwent GCRA at the time of their breast cancer diagnosis. The mean age of women undergoing GCRA during a breast cancer diagnosis was 43 years (range, 27-62 years). Subjects underwent GCRA at a mean period of 27 days (range, 3-72 days) after initial diagnosis. Two women had a low prior probability (<8%) of *BRCA1* or *BRCA2* mutation detection and therefore decided against genetic testing. The remaining 35 women had a 23% mean probability (range, 10%-84%) of a deleterious mutation in one of the *BRCA* genes being responsible for their breast cancer. Three women declined genetic testing because of psychological stressors concurrent with their breast cancer diagnoses. Of the remaining 32 women who chose to proceed with genetic analysis, 22 (69%) had negative test results and a mean pretest mutation probability of 22%, 3 (9%) had a VUS, and 7 (22%) were found to have deleterious mutations in the *BRCA1* or *BRCA2* gene. The latter group had a mean pretest probability of 40%. Two women with negative test results opted for bilateral mastectomy, citing persistent fear of a second breast cancer. In each case, the clinical judgment according to pedigree analysis was that their cancers were most likely sporadic given the negative test results. The 20 remaining women with negative test results received stage-appropriate treatment. None of the patients with a negative test result had a pedigree suggestive of the phenotype of hereditary breast and ovarian cancer, which might otherwise have warranted counseling about the high genetic risk of new primary tumors. The χ^2 analysis indicated a significant effect ($P<.001$) for the influence of *BRCA* test results on the use of concurrent risk reduction (bilateral) surgery compared with a unilateral surgical procedure (**Table 1**).

Table 1. Effect of *BRCA* Test Results on Surgical Choices*

BRCA Gene Mutation Status	Bilateral Surgical Procedure (Therapeutic and Risk Reduction)	Unilateral Surgical Procedure (Therapeutic Only)
Positive	7	0
Negative	2	20

Abbreviation: *BRCA*, breast cancer gene.
*χ^2_1=16.48 ($P<.001$).

Three women in whom a VUS was identified were counseled as though their results were uninformative. Nevertheless, 1 of the 3 chose bilateral mastectomy, citing persistent fear of cancer and the uncertainty associated with the finding of a VUS. Her pretest probability was 25%. The VUS cases were excluded from further analysis because of potential ambiguity about the interpretation of test results. However, the effect of a positive result on definitive surgical choices remained highly significant even if the VUS cases were included in the negative result category ($P=.001$).

The profiles and treatment decisions of the 7 women who had a positive test result for a deleterious *BRCA* mutation are summarized in (**Table 2**). Two had previously undergone BCT for unilateral breast cancer; one had a contralateral breast cancer 2 years after her initial diagnosis at age 27 years, and the other was diagnosed as having a contralateral breast cancer 3 years after her initial diagnosis at age 40 years. Both of these patients were clinically eligible for another BCT procedure but chose bilateral mastectomy in light of their positive test results. Each expressed regret that they had not undergone GCRA at the time of their first diagnoses because their treatment decisions might have been different and they would likely have avoided a second breast cancer.

Table 2. *BRCA1/BRCA2* Mutation Carrier Profiles*

Age, y	Stage	Mutation Probability, %	Mutation Detected	Treatment Choice	Comment
29	II	35	*BRCA1* IVS5-12 A to G	RRM	BCT for previous breast cancer
43	I	24	*BRCA1* 5385insC	RRM + RRSO	BCT for previous breast cancer
36	II	50	*BRCA1* 185delAG	RRM	
56	I†	50‡	*BRCA1* 185delAG	RRM	
43	I	45	*BRCA2* 254delC	RRM + RRSO	
47	I†	28	*BRCA2* 6174delT	RRM	
39	II	50	*BRCA1* 185delAG	RRM	

Abbreviations: BCT, breast-conserving therapy; *BRCA*, breast cancer gene; RRM, risk reduction mastectomy[28]; RRSO, risk reduction salpingo-oophorectomy.
*Pathologic stage was determined according to the *American Joint Committee on Cancer Staging Manual*.
†Clinical stage as nodal status was not known at the time of referral for genetic cancer risk assessment.
‡Mendelian risk was 50%; breast cancer diagnosis indicates more than a 50% probability of a mutation.

Certainly their experience with the first cancer may have influenced the choice of risk reduction mastectomy after learning of their positive test results. However, the effect of a positive result on definitive surgical choices remained highly significant when the second primary cases were excluded from the analysis. Two of the 7 women also opted for concurrent risk reduction salpingo-oophorectomy.

The 32 women who proceeded with *BRCA* gene testing at the time of diagnosis underwent GCRA at various points during the initial treatment of their breast cancer. Eleven women underwent GCRA immediately following the results of a biopsy (excisional, core, or fine needle aspiration). Eleven women enrolled for GCRA after definitive breast-conserving surgery and reported prior to GCRA that they were deciding between completion mastectomy and radiation therapy. Five of these women were being treated with adjuvant chemotherapy. Four women underwent unilateral mastectomy and were also undergoing adjuvant chemotherapy. Three women had undergone a biopsy and were scheduled to begin chemotherapy at the time of the GCRA consultation. Two women underwent GCRA at the completion of chemotherapy. One woman underwent GCRA at the scheduled start of radiation therapy and chose to postpone therapy to obtain the results. In no other case was definitive therapy delayed to accommodate genetic testing. Finally, a comparison of the model-predicted prior probability of a *BRCA* gene mutation with the results of genetic analyses in this cohort demonstrated a strong correlation (23% predicted and 22% detected), although the study was not designed to test the validity of the commonly used prediction models.

COMMENT

The value of GCRA at diagnosis is illustrated through this prospective study of women newly diagnosed as having breast cancer. Most patients referred for GCRA at the time of diagnosis were appropriately referred: 35 (95%) of 37 had an estimated *BRCA* mutation probability that warranted testing. Only 2 women of the 37 referred during diagnosis declined genetic testing because of the low probability of mutation detection. The use of risk reduction surgery concurrent with therapeutic surgical treatment of breast cancer was significantly higher among women who carried a deleterious *BRCA* gene mutation compared with those who received negative or noninformative (VUS) results. That virtually all of the women with a *BRCA* mutation in this study chose concurrent risk reduction surgery is striking. Many of the 106 patients with breast cancer who underwent GCRA after the completion of therapy expressed regret that they did not have this opportunity at the time of their initial diagnosis, and a formal study of their outcomes is ongoing.

Published observations of unaffected *BRCA* mutation carriers indicate that 17% to 50% opt for risk reduction breast surgery.[25,26,35,36] To our knowledge, there are no published studies of the risk reduction surgery choices of women who are determined to be *BRCA* carriers after the completion of breast cancer treatment, although one recent prospective study reported a rate of 15% for both unaffected and affected carriers.[25] Preliminary results of a study of 150 women previously treated for breast cancer, who later underwent GCRA and genetic testing by the same team, indicated that 16 (44%) of 36 *BRCA* carriers chose risk reduction surgery in the face of their increased risk for a new primary breast cancer (D.J.M. and J.N.W., unpublished data, 2003). The reasons for the difference in use of risk reduction surgery may include the convenience of being able to pursue this option without the necessity of a separate anesthesia, hospitalization, and recovery period associated with subsequent surgery performed exclusively for risk reduction. In addition, treatment options in the setting of an ipsilateral second primary breast cancer are limited; mastectomy is usually obligatory if the breast has previously undergone irradiation as part of BCT for the initial diagnosis. In some cases, advanced radiotherapeutic techniques may allow retreatment. Furthermore, the quality of subsequent reconstruction may be compromised by prior treatment. Thus, genetic information at diagnosis may allow women to be proactive about their choices for initial surgical treatment by incorporating both current and future cancer risk into their decision-making process.

It is possible that there was some bias by the treating physicians toward the referral of patients who were more likely to consider risk reduction procedures. Factors that are thought to influence decisions about risk reduction surgery include quality of surveillance mea-

sures, family cancer experiences, marital status, and the presence of young children. It is also possible that additional psychological factors such as overwhelming fear in the immediacy of a new breast cancer diagnosis may influence women to make more dramatic surgical choices. Understanding to what extent these and other factors influence risk management decisions is an important area for future studies.

Counseling with respect to breast cancer risk, especially for patients who have negative or uninformative results, must take into consideration the potential limitations of testing and the possibility of other hereditary breast cancer syndromes. Patients with a strong family history of breast cancer and negative or uninformative results may have second primary breast cancer risk estimates that exceed the 20% risk in sporadic disease. In selected patients, prophylactic mastectomy may be a risk reduction treatment option regardless of the *BRCA* test result. The importance of working with an experienced, knowledgeable GCRA team is stressed.

Although GCRA may be a valuable component of care for some women newly diagnosed as having breast cancer, logistical issues can be challenging. Women in this study underwent GCRA at various points during their initial breast cancer diagnosis and treatment. In some cases primary surgical therapy had not yet been initiated, whereas other patients were nearing the end of chemotherapy and deciding between completion mastectomy vs radiation therapy. The window of opportunity to affect treatment decisions is essentially the time between complete tumor resection and initiation of radiotherapy if BCT is planned; GCRA can be conducted during adjuvant chemotherapy, which is offered to many premenopausal patients with breast cancer. The capacity to initiate the GCRA process within days to weeks of a referral is necessary to integrate the resulting genetic risk information into the treatment-planning process without delaying primary therapy. Comprehensive GCRA is a multistep process encompassing pedigree construction and analysis, risk assessment, informed consent, disclosure of results, and provision of risk-appropriate recommendations. *BRCA* gene sequencing in the commercial setting averages 3 to 4 weeks following the receipt of a blood specimen. Delays in obtaining insurance authorization for *BRCA* gene analysis can prolong this process. Results are normally given in person, and arranging a follow-up visit to coincide with the receipt of results can be challenging.

For many patients with newly diagnosed breast cancer, decisions regarding definitive surgical therapy may be influenced by knowledge of the presence or absence of a deleterious mutation. Our cohort of women reflects a highly motivated group who followed through with recommendations for GCRA and opted to proceed with testing in most cases. The proportion of women who decline counseling owing to a lack of resources or fear of discrimination is unknown; the risk management choices made by other less risk-averse women might be different. Emerging data about breast cancer risk reduction associated with salpingo-oophorectomy in premenopausal *BRCA* carriers may influence some women's choices.[32] To be integrated into the initial breast cancer treatment, GCRA is best performed in a proximal time frame during adjuvant chemotherapy, following extirpation of a primary tumor, or in the setting of neoadjuvant chemotherapy. Because effective treatment of newly diagnosed breast cancer is likely to have the greatest influence on overall survival,[37] initial surgical treatment should not be unnecessarily delayed.

Genetic cancer risk assessment at breast cancer diagnosis can determine who is appropriate to test, evaluate the probability that a mutation in the *BRCA1* or *BRCA2* gene is responsible for disease in women with newly diagnosed breast cancer, interpret genetic-testing results, and provide risk-appropriate recommendations for the management of future cancer risk based on genetic analysis. In most cases, GCRA influenced surgical decision making in a risk-appropriate way and should be considered as a standard-of-care option for any woman with newly diagnosed breast cancer and a reasonable probability of *BRCA* gene mutation. More research is needed to elucidate the reasons for the significant difference observed in use of risk reduction surgery when genetic knowledge was made available at the time of a new breast cancer diagnosis and to determine the optimal time to perform GCRA.

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