Published in final edited form as:
Ann Surg Oncol. 2008 December ; 15(12): 3415–3421. doi:10.1245/s10434-008-0160-3.

Contralateral Risk-Reducing Mastectomy in Young Breast Cancer Patients with and without Genetic Cancer Risk Assessment

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Abstract

Background—Decisions regarding contralateral risk-reducing mastectomy (CRRM) among women diagnosed with unilateral breast cancer can potentially be influenced by age at diagnosis and other factors. In this study, we examined the use of CRRM before versus after genetic cancer risk assessment (GCRA) in women diagnosed with breast cancer before age 50.

Methods—We conducted a retrospective analysis of women with invasive breast cancer diagnosed before age 50 who were seen for GCRA between October 1996 and March 2005. Associations between the presence of generally accepted indications for risk-reducing surgery among women who had CRRM and the timing of GCRA were examined.

Results—The cohort included 378 women, of whom 57 had CRRM pre-GCRA and 45 had CRRM post-GCRA after a median follow-up of 26 months. Women who had CRRM pre-GCRA were more likely to not have a generally accepted indication for the procedure than those who did after GCRA (odds ratio [OR] 5.3, 95% confidence interval [95% CI] 1.6–17.8, $P = .007$). Women diagnosed with breast cancer before *BRCA* genetic testing became clinically available (1997) were more likely to have had CRRM pre-GCRA than those who were diagnosed more recently (OR 2.9, 95% CI 1.6–5.2, $P = .0003$).

Conclusion—When personal and family history was carefully examined, a substantial proportion of women seen in our clinic did not have a clear indication for CRRM. Decreased use of empiric CRRM among women diagnosed after 1997 may indicate increased awareness and use of GCRA. Thus, judicious application of GCRA may help focus use of surgical risk reduction measures to the most risk-appropriate patients.

Breast cancer is the most common cancer among women in the United States, with approximately 182,500 new diagnoses expected in 2008.[1] Approximately 5–10% of all breast cancer cases (10,000–20,000 new cases/year) are associated with germline mutations in highly penetrant genes.[2,3] Germline mutations in the hereditary breast and ovarian cancer-associated genes, *BRCA1* and *BRCA2*, are associated with a 56–87% lifetime risk of developing breast cancer.[4–9] Breast cancer patients with a germline *BRCA* mutation have an approximately 40–50% risk of developing a second primary breast cancer in the remaining at-risk breast tissue, with higher risk observed in patients whose initial cancer was diagnosed

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at an earlier age.[8,10–12] Other hereditary breast cancer syndromes include Li-Fraumeni syndrome (*p53* gene)[13] and Cowden syndrome (*PTEN* gene).[14] Risk-reducing mastectomy has been shown to lower the risk of developing breast cancer in *BRCA* mutation carriers by greater than 90%[10,15–17] and is considered an appropriate option for care in this setting. However, although contralateral risk-reducing mastectomy (CRRM) has been shown to reduce the risk for new primary breast cancer in women previously diagnosed with unilateral breast cancer,[18–20] its effect on breast cancer specific and overall mortality among those without a known deleterious *BRCA* mutation has not been clearly established.[21,22]

Before genetic testing for the *BRCA1* and *BRCA2* genes became commercially available, CRRM was often considered based on clinical indications, such as diffuse microcalcifications, prior or concurrent history of lobular carcinoma in situ (LCIS), large and difficult-to-examine breasts, breast cancer risk factors such as atypical hyperplasia, family history of breast cancer in a first-degree relative, and young age at diagnosis (<40 years).[23] Family history and perceived high risk for a new primary breast cancer have often been cited as reasons for choosing CRRM.[19,24] However, some women have reported regretting the decision to pursue empiric CRRM,[24] and detailed evaluation of family and personal cancer diagnoses might not substantiate perceived increased risk. In a study investigating the predictors of CRRM among women with unilateral breast cancer seen for risk assessment, early age at breast cancer diagnosis, less than full-time employment, and having one or more first-degree relative with breast cancer or ovarian cancer were among the factors identified to be associated with having CRRM prior to genetic counseling and testing; however, only a small number of these women turned out to carry a *BRCA* mutation.[25] With the availability of genetic testing for *BRCA1* and *BRCA2* genes, women newly diagnosed with breast cancer have the option, if indicated, of undergoing genetic cancer risk assessment (GCRA) for a more accurate evaluation of new primary breast cancer risk. In this study, we compared women diagnosed with breast cancer before age 50 years who had CRRM prior to GCRA to those who chose the procedure after GCRA.

METHODS

The study population comprises women diagnosed with breast cancer before age 50, seen for GCRA in the City of Hope Cancer Screening & Prevention Program Network (CSPPN) and enrolled in an Institutional Review Board-approved registry protocol between October 1996 and March 2005. Approximately 98% of women attending the CSPPN enroll in the registry.[26] Women with documented metastatic or synchronous bilateral disease at diagnosis were excluded (n = 11). For women with more than one primary breast cancer diagnosed at different times, we used the most recent diagnosis at which the option of CRRM was applicable, but took into account the age at diagnosis for the earliest cancer. Medical records and a baseline questionnaire obtained prior to the first visit provided information on past personal medical history, including all cancer diagnoses, treatments received, and any risk-reducing interventions. A detailed family history over at least three generations was obtained at the initial GCRA visit.

For patients who had CRRM prior to the visit, indication(s) for the procedure was elucidated from the patients and medical records when available. All subjects received GCRA by a team consisting of a genetic cancer risk counselor and a geneticist–oncologist. In addition to a thorough review of personal and family history, the GCRA session also included a discussion of basic cancer genetics principles, the patient's estimated probability of having hereditary breast cancer based on personal and family history, and the potential benefits, risks, and limitations of genetic testing. The probability of mutation was given as a range based on estimations obtained from the mathematical models available at the time of evaluation. [27–29] No threshold was used as a cut-off for recommending testing, as consistent

with the updated ASCO policy statement.[30] All genetic testing was performed in Clinical Laboratory Improvement Amendments (CLIA)-approved laboratories (*BRCA* gene sequencing at Myriad Genetics Laboratory, Salt Lake City, UT; *p53* gene sequencing at City of Hope Clinical Molecular Diagnostic Laboratory, Duarte, CA; *PTEN* gene sequencing at Ohio State University, Columbus, OH). At a follow-up visit, test results were disclosed and new primary breast cancer risk estimates, based on mutation carrier status or empiric risk factors, and management options according to risk levels were discussed. A follow-up mailed questionnaire was administered at least a year after the initial visit to obtain updates on personal and family cancer history, to evaluate adherence to surveillance recommendations, and to assess risk-reducing intervention choices. Patients reporting CRRM after their initial visit were asked to list the reasons that influenced their surgical decision.

Of the 378 patients included in this study, 4 (1%) died before a follow-up questionnaire was obtained and 12 (3%) were lost to follow-up. Prospective data on risk-reduction intervention choices were abstracted from available medical records for 109 of 164 patients who did not return the follow-up questionnaire, leaving a total of 67 (18%) with no followup data. Use of human subject data in this study was approved by the City of Hope Institutional Review Board in accordance with an assurance filed with and approved by the Department of Health and Human Services.

We categorized family history into strong, any, and none. Strong family history was defined as having a family history of at least two first- or second-degree relatives with breast cancer diagnosed before the age of 50 or at least one first- or second-degree relative with breast cancer diagnosed before the age of 50 and at least one first- or second-degree relative with ovarian cancer diagnosed at any age. Any family history includes those with a family history of breast and/or ovarian cancer that did not meet the criteria for strong family history. We defined accepted clinical indications for CRRM, adapted in part from Society of Surgical Oncology position statements on prophylactic mastectomy in 1993,[23] as one of the following: age at diagnosis <40 years, lobular histology of primary breast cancer, a strong family history, contralateral breast benign findings, and practical reconstruction considerations, or positive mutation carrier status for those who had CRRM post-GCRA. A result of a variant of unknown significance (VUS) was carefully evaluated using available ancillary data (e.g., observations with deleterious mutations in the same gene, tracking data, and degree of evolutionary conservation for the given amino acid substitution, etc.). None of the VUS in this study were suggestive of a deleterious change. Furthermore, none of the participants with a VUS in this study had a family history that was phenotypically consistent with hereditary breast/ovarian cancer even in the absence of an identified deleterious mutation. Thus, all of the VUS were considered uninformative and grouped with negative test results in all analyses.

Baseline characteristics across groups were compared using chi-square or Fisher's exact tests for categorical variables and Wilcoxon tests for continuous variables. For women who had risk-reducing surgery, we examined the association between timing of CRRM (before vs after GCRA) and the presence of the generally accepted indications for CRRM as defined previously using logistic regressions. We also examined the likelihood of having CRRM prior to GCRA among women who were diagnosed before January 1997 compared with those who were diagnosed later. Age at diagnosis was included in all logistic regression models. Odds ratios and two-sided *P* values are reported. All statistical analyses were performed with SAS version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

The cohort included 378 women, of whom 57 had CRRM prior to GCRA, 45 had CRRM after GCRA, and 276 did not have CRRM. By design, all women in the eligible cohort were younger than age 50 years at diagnosis. The median age at diagnosis was 40 years overall, with no significant differences in age distribution noted between women who had CRRM pre-GCRA, those who had CRRM post-GCRA, and those who did not have CRRM (Table 1). Age at diagnosis was not associated with having CRRM prior to GCRA ($P = .93$). There was also no significant difference in tumor histology distribution across the three groups ($P = .34$).

Women who had CRRM post-GCRA were more likely to have a strong family history compared with those who had CRRM pre-GCRA (42.2% vs 17.5%, $P<.02$). Of the 336 women who had genetic testing, 3 had testing for the *p53* gene, 1 had testing for the *PTEN* gene, and 332 had testing for the *BRCA1* and *BRCA2* genes, either with full sequencing, the three Ashkenazi Jewish founder mutations, or a known familial mutation. Of all those tested, 74 (22.0%) were found to have a deleterious mutation. Of the 46 women who had CRRM pre-GCRA and chose to pursue genetic testing as part of GCRA, 11 (23.9%) were subsequently identified to carry a deleterious mutation (10 in *BRCA1* or *BRCA2* and 1 in *p53*). On the other hand, of the 44 women who chose CRRM after having GCRA and genetic testing, 34 (77.3%) had a deleterious mutation in one of the two *BRCA* genes. Of the 248 women without CRRM who had genetic testing, 29 (11.7%) were found to have a deleterious mutation (27 in *BRCA1* or *BRCA2*, 1 in *p53*, and 1 in *PTEN*) (Table 1).

At the time of genetic evaluation, 39 of the 57 women who had CRRM prior to GCRA (68.4%) were found to have at least one of the clinical indications for empiric CRRM (Table 2). Women who had CRRM post-GCRA were significantly more likely to have an indication for the procedure compared with those who had CRRM pre-GCRA (OR 5.3, 95% CI 1.6–17.8, $P = .007$) (Table 3). The median time between diagnosis and risk-reduction mastectomy was significantly shorter for women who had CRRM prior to GCRA compared with those who had CRRM after having GCRA, both for the entire cohort (1.5 months vs 23.2 months, $P<.001$) and when the analysis was restricted to only those who were diagnosed after January 1997, approximately the time when commercial genetic testing for *BRCA1* and *BRCA2* genes became widely available in the clinical setting (1.6 months vs 11.6 months, $P = .005$).

Of the 378 women in this study, 131 were diagnosed before and 247 were diagnosed after January 1997. Women who were diagnosed with breast cancer before January 1997 were approximately three times more likely to undergo CRRM prior to GCRA compared with those who were diagnosed after January 1997 (24.4% vs 10.1%, OR 2.9 95%, CI 1.6–5.2, $P = .0003$) (Table 4).

DISCUSSION

Perceived high risk for a new primary breast cancer has often been cited as a reason for considering risk-reduction surgical intervention in women diagnosed with breast cancer.[19,24] Our study showed that women who had CRRM prior to GCRA were more likely to not have an indication for the procedure compared with those who had CRRM after GCRA. We chose the 1993 Society of Surgical Oncology position statements on prophylactic mastectomy, and not the recently updated statements, as the generally accepted indications because they were the clinical guidelines for consideration of CRRM available during the time period under study. Our finding suggests that GCRA, with expert counseling after careful examination of family history and personal risk profile for a second primary breast

cancer prior to decision making, may reduce unwarranted CRRM in young breast cancer patients. This conclusion is also supported by the finding that among our primarily referral-based cohort, the use of empiric CRRM was lower for young patients diagnosed with breast cancer after January 1997, when commercial genetic testing for *BRCA1* and *BRCA2* became widely available, compared with those diagnosed before January 1997.

Although contralateral risk-reducing mastectomy has been shown to decrease the incidence of a new primary breast cancer in women previously diagnosed with unilateral breast cancer,[19,20] its impact on survival is not well established.[21,22] Thus, CRRM may not be appropriate for all women diagnosed with a primary breast cancer. Among women who have had unilateral breast cancer, the risk of developing a new primary breast cancer after the initial diagnosis is approximately 0.5–1% per year, with higher risk associated with certain characteristics such as younger age at diagnosis and lobular histology of the primary tumor.[31] In the updated position statement on prophylactic mastectomy recently released by the Society of Surgical Oncology, consideration for CRRM was recommended for (1) risk reduction in high-risk patients based on *BRCA* mutation status or a strong family history, (2) difficult surveillance (either clinical or radiological findings), and (3) reconstructive concerns.[32] A recent report based on the Surveillance, Epidemiology and End Results (SEER) database showed that the rate of CRRM among patients diagnosed with unilateral breast cancer increased steadily from 1998 to 2003.[33] However, information on factors that may have influenced patients' surgical decision, such as family history, genetic counseling and testing, mammographic findings, and reconstructive issues, were not available. Furthermore, the reason for undergoing risk-reducing surgery could not be obtained from the SEER database. Thus, it is difficult to assess what proportion of these surgeries was risk-appropriate.

In a retrospective study of 296 women with breast cancer who had had CRRM, 14% of the women indicated "fear of developing more breast cancer" based on perceived risk as the reason for the having the procedure.[24] However, this cohort included women with a wide range of ages who did not have formal GCRA prior to making their decisions. Several studies have shown that a woman's perceived risk of breast cancer is often higher than objective estimated risk based on known risk factors.[34–38] Early age at breast cancer diagnosis was also observed to be associated with having CRRM prior to GCRA in a similar study.[25] Although we did not observe any association between the decision to have CRRM and age at diagnosis, we only included women diagnosed before the age of 50 in our study cohort and thus cannot generalize this observation to other age ranges. Genetic cancer risk assessment, which includes a thorough examination of family history and personal risk factors and possibly genetic testing, may provide a more accurate estimation of second primary breast cancer risk than based on age at diagnosis alone, which may play an important role in the risk-reduction decision-making process for women with early onset breast cancer.

Although genetic testing for *BRCA1* and *BRCA2* became commercially available in 1996, barriers to access have included concerns about potential harms and genetic discrimination,[39,40] initial lack of clearly established indications for testing, and unproven benefits of interventions. Nonetheless, with accumulating evidence for screening and risk-reduction interventions and clearer referral guidelines, genetic counseling and *BRCA* genetic testing when appropriate have demonstrated utility in risk assessment and have become the standard of care for women whose family and/or personal history are suspicious for a hereditary etiology.[41–43] The lower proportion of women undergoing CRRM prior to GCRA among those diagnosed after January 1997 compared with those diagnosed prior to January 1997 in our study may indicate increased awareness and utilization of GCRA among health care practitioners.

Our study has several limitations. First, information on the indications for considering CRRM was either elicited during the GCRA consultative process or abstracted from chart review and not prospectively collected prior to the procedure for the cases that had CRRM prior to GCRA. Furthermore, we did not have complete information on stage at diagnosis or initial surgical therapy required, which may influence the decision for CRRM.

Second, our cohort was collected from a primarily referral-based clinical practice, and one cannot exclude some referral bias. Certainly many patients who have empiric CRRM are not referred for risk evaluation at all, resulting in an underestimation of the number of women who make this decision without the benefit of formal GCRA. Although family history of breast and/or ovarian cancer was cited as the basis for undergoing CRRM prior to GCRA for many patients in this study, upon thorough evaluation the objective risk was often not as high as perceived. Thus, it is possible that among all young patients who had pre-GCRA CRRM, the actual proportion not having a generally accepted clinical indication differs from that observed in our cohort. Furthermore, the study population was mainly from the Southern California area and may not be representative of the rest of the country; thus, our findings might not be generalizable to all women.

The vast majority of participants in our study were accrued before availability of commercial testing for *BRCA1* and *BRCA2* genomic rearrangements. It is possible that a rearrangement was present in some of the women who tested negative for a deleterious mutation by sequencing only. Thus, some of the participants who had CRRM without an apparent indication could in fact have been mutation positive. Also, although the three founder mutations account for most of the mutations identified in individuals of Ashkenazi Jewish descent, a missed mutation is potentially a possibility among women with Ashkenazi Jewish ancestry who only had testing for these three mutations. However, not all women of Ashkenazi Jewish ancestry in our study had testing for only the three *BRCA* founder mutations; depending on their family history and other factors; some did choose to have full sequencing performed. Thus, we believe that the likelihood of a missed mutation in this subgroup is small.

Our study also has several strengths. The City of Hope Cancer Screening & Prevention Program Network is a well-known cancer genetics clinic at a major cancer center with a large referral base in Southern California. Personal and family history was collected uniformly using a standardized questionnaire from all participants. Furthermore, a detailed pedigree with at least three generations and family history information was obtained for all participants during the initial clinic visit. Updates regarding surgical interventions after GCRA were obtained from a follow-up questionnaire administered at least 1 year after the initial clinic visit and medical records.

New data supporting the efficacy of alternative interventions such as intensive surveillance and chemoprevention might also influence decisions about CRRM. Women are more likely to be satisfied with their decision to have CRRM, and with the outcome of the procedure, if they played an active role in the initial decision-making process.[44] Thus, prior to making a decision to undergo CRRM, women should have the benefit of a comprehensive evaluation of family history and personal risk factors for risk estimation, a discussion of medical and psychological benefits and consequences of risk-reducing surgeries, as well as a thorough discussion of other risk-reducing and surveillance options.

In summary, our study indicates that judicious application of GCRA for patients diagnosed with breast cancer at a young age could provide a more accurate estimation for new primary breast cancer risk and may promote more risk-appropriate interventions and reduce unwarranted contralateral risk-reducing mastectomy.

Acknowledgments

This study was supported in part by NIH grant No. R25 CA85771 and by a General Clinical Research Center grant from NIH (M01 RR00043) awarded to the City of Hope National Medical Center, Duarte, CA. The authors would like to express their deepest appreciation to all of the participants in our hereditary cancer registry, without whom this study could not have been accomplished. We are also indebted to Bersabell Asaye and Sharon Sand for their research support.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2008. CA Cancer J Clin 2008;58:71–96. [PubMed: 18287387]
2. Newman B, Austin MA, Lee M, et al. Inheritance of human breast cancer: evidence for autosomal dominant transmission in high-risk families. Proc Natl Acad Sci USA 1988;85:3044–8. [PubMed: 3362861]
3. Newman B, Mu H, Butler LM, et al. Frequency of breast cancer attributable to BRCA1 in a population-based series of American women. JAMA 1998;279:915–21. [PubMed: 9544765]
4. Ford D, Easton DF, Bishop DT, et al. Risks of cancer in BRCA1-mutation carriers. Lancet 1994;343:692–5. [PubMed: 7907678]
5. Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Am J Hum Genet 1995;56:265–71. [PubMed: 7825587]
6. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997;336:1401–8. [PubMed: 9145676]
7. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. Am J Hum Genet 1998;62:676–89. [PubMed: 9497246]
8. Brose MS, Rebbeck TR, Calzone KA, et al. Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst 2002;94:1365–72. [PubMed: 12237282]
9. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003;302:643–6. [PubMed: 14576434]
10. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22:2328–35. [PubMed: 15197194]
11. The Breast Cancer Linkage Consortium. Cancer risks in *BRCA2* mutation carriers. J Natl Cancer Inst 1999;91:1310–6. [PubMed: 10433620]
12. Verhoog LC, Brekelmans CT, Seynaeve C, et al. Contralateral breast cancer risk is influenced by the age at onset in BRCA1-associated breast cancer. Br J Cancer 2000;83:384–6. [PubMed: 10917555]
13. Olivier M, Goldgar DE, Sodha N, et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res 2003;63:6643–50. [PubMed: 14583457]
14. Schreibman IR, Baker M, Amos C, et al. The hamartomatous polyposis syndromes: a clinical and molecular review. Am J Gastroenterol 2005;100:476–90. [PubMed: 15667510]
15. 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;22:1055–62. [PubMed: 14981104]
16. Meijers-Heijboer H, van Geel B, van Putten WLJ, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2001;345:159–64. [PubMed: 11463009]
17. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst 2001;93:1633–7. [PubMed: 11698567]
18. McDonnell SK, Schaid DJ, Myers JL, et al. Efficacy of contralateral prophylactic mastectomy in women with a personal and family history of breast cancer. J Clin Oncol 2001;19:3938–43. [PubMed: 11579114]

19. Herrinton LJ, Barlow WE, Yu O, et al. Efficacy of prophylactic mastectomy in women with unilateral breast cancer: a Cancer Research Network project. J Clin Oncol 2005;23:4275–86. [PubMed: 15795415]
20. Peralta EA, Ellenhorn JD, Wagman LD, et al. Contralateral prophylactic mastectomy improves the outcome of selected patients undergoing mastectomy for breast cancer. Am J Surg 2000;180:439–45. [PubMed: 11182394]
21. Tuttle T, Habermann E, Abraham A, et al. Contralateral prophylactic mastectomy for patients with unilateral breast cancer. Expert Rev Anticancer Ther 2007;7:1117–22. [PubMed: 18028020]
22. Quan G, Pommier SJ, Pommier RF. Incidence and outcomes of contralateral breast cancers. Am J Surg 2008;195:645–50. [PubMed: 18424281]
23. Bilimoria MM, Morrow M. The woman at increased risk for breast cancer: evaluation and management strategies. CA Cancer J Clin 1995;45:263–78. [PubMed: 7656130]
24. Montgomery LL, Tran KN, Heelan MC, et al. Issues of regret in women with contralateral prophylactic mastectomies. Ann Surg Oncol 1999;6:546–52. [PubMed: 10493622]
25. Graves K, Peshkin B, Halbert C, et al. Predictors and outcomes of contralateral prophylactic mastectomy among breast cancer survivors. Breast Cancer Res Treat 2007;104:321–9. [PubMed: 17066320]
26. MacDonald DJ, Sand S, Kass FC, et al. The power of partnership: Extending comprehensive cancer center expertise in clinical cancer genetics to breast care in community centers. Semin Breast Dis 2006;9:39–47.
27. Couch FJ, DeShano ML, Blackwood MA, et al. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med 1997;336:1409–15. [PubMed: 9145677]
28. Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. J Clin Oncol 2002;20:1480–90. [PubMed: 11896095]
29. Parmigiani G, Berry D, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. Am J Hum Genet 1998;62:145–58. [PubMed: 9443863]
30. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol 2003;21:2397–406. [PubMed: 12692171]
31. Broet P, de la Rochefordiere A, Scholl SM, et al. Contralateral breast cancer: annual incidence and risk parameters. J Clin Oncol 1995;13:1578–83. [PubMed: 7602346]
32. Giuliano A, Boolbol S, Degnim A, et al. Society of Surgical Oncology: Position statement on prophylactic mastectomy. Approved by the Society of Surgical Oncology Executive Council, March 2007. Ann Surg Oncol 2007;14:2425–7. [PubMed: 17597344]
33. Tuttle TM, Habermann EB, Grund EH, et al. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: A trend toward more aggressive surgical treatment. J Clin Oncol 2007;25:5203–9. [PubMed: 17954711]
34. van Dijk S, Otten W, Zoeteweij MW, et al. Genetic counselling and the intention to undergo prophylactic mastectomy: effects of a breast cancer risk assessment. Br J Cancer 2003;88:1675–81. [PubMed: 12771979]
35. Evans DG, Blair V, Greenhalgh R, et al. The impact of genetic counselling on risk perception in women with a family history of breast cancer. Br J Cancer 1994;70:934–8. [PubMed: 7947100]
36. Dolan NC, Lee AM, McDermott MM. Age-related differences in breast carcinoma knowledge, beliefs, and perceived risk among women visiting an academic general medicine practice. Cancer 1997;80:413–20. [PubMed: 9241075]
37. Black WC, Nease RF Jr, Tosteson ANA. Perceptions of breast cancer risk and screening effectiveness in women younger than 50 years of age. J Natl Cancer Inst 1995;87:720–31. [PubMed: 7563149]
38. Lerman C, Lustbader E, Rimer B, et al. Effects of individualized breast cancer risk counseling: a randomized trial. J Natl Cancer Inst 1995;87:286–92. [PubMed: 7707420]
39. Cho MK, Sankar P, Wolpe PR, et al. Commercialization of BRCA1/2 testing: Practitioner awareness and use of a new genetic test. Am J Med Genet 1999;83:157–63. [PubMed: 10096590]
40. Collins FS. BRCA1—Lots of mutations, lots of dilemmas. N Engl J Med 1996;334:186–8. [PubMed: 8531977]

41. ASCO. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol 2003;21:2397–406. [PubMed: 12692171]

42. Guillem JG, Wood WC, Moley JF, et al. ASCO/SSO review of current role of risk-reducing surgery in common hereditary cancer syndromes. J Clin Oncol 2006;24:4642–60. [PubMed: 17008706]

43. Daly MB, Axilbund JE, Bryant E, et al. Genetic/Familial high-risk assessment: breast and ovarian. J Natl Compr Canc Netw 2006;4:156–76. [PubMed: 16451772]

44. Nekhlyudov L, Bower M, Herrinton LJ, et al. Women's decision-making roles regarding contralateral prophylactic mastectomy. J Natl Cancer Inst Monogr 2005;35:55–60. [PubMed: 16287886]

TABLE 1

Characteristics of women with pre-GCRA CRRM, post-GCRA CRRM, and no CRRM

Characteristics	Pre-GCRA CRRM	Post-GCRA CRRM	No CRRM	Total
Total number	57	45	276	378
Median age at diagnosis (range)	40 (22–49)	39 (27–49)	41 (21–49)	40 (21–49)
Histology (%)				
Ductal	50 (87.7)	41 (90.7)	259 (93.9)	350 (92.6)
Lobular	5 (8.8)	2 (4.6)	9 (3.2)	16 (4.2)
Mixed, other, or unknown	2 (3.5)	2 (4.6)	8 (2.9)	12 (3.2)
Family history[a] (%)				
None or adopted	12 (21.0)	7 (15.6)	74 (26.8)	93 (24.6)
Any	35 (61.4)	19 (44.2)	169 (61.2)	223 (59.0)
Strong	10 (17.5)	19 (42.2)	33 (12.0)	62 (16.4)
Genetic test result (%)				
Deleterious mutation	11 (19.3)	34 (76.7)	29 (10.4)	74 (19.6)
No mutation found	32 (56.1)	8 (18.6)	191 (69.1)	231 (61.1)
Variant of unknown significance	3 (5.3)	2 (2.3)	26 (9.7)	31 (8.2)
Not done	11 (19.3)	1 (2.3)	30 (10.8)	42 (11.1)

[a] Strong family history: ≥2 first- or second-degree relatives (F/SDR) with breast cancer before age 50 or ≥1 F/SDR with breast cancer before age 50 *and* ≥1 F/SDR with ovarian cancer at any age.

GCRA, genetic cancer risk assessment; CRRM, contralateral risk-reducing mastectomy.

TABLE 2

Time interval between diagnosis and CRRM and indications for CRRM

	CRRM		
	Pre-GCRA (*n* = 57)	**Post-GCRA (*n* = 45)**	***P* value**
Median time, in months, from diagnosis to CRRM (range)	1.5 (0–168)	23.2 (0.1–332)	<.001
Indication for CRRM[a] (%)	39 (68.4)	41 (91.1)	
Age younger than 40	27	22	
Strong family history	10	19	
ILC histology	6	2	
Reconstruction considerations	0	2	
Contralateral benign findings	5	1	
Deleterious mutation carriers	0	34	
No indication (%)	18 (31.6)	4 (8.9)	

[a] Some participants have more than one indication for having CRRM.

GCRA, genetic cancer risk assessment; CRRM, contralateral risk-reducing mastectomy; ILC, infiltrating lobular carcinoma.

Strong family history: ≥2 first- or second-degree relatives (F/SDR) with breast cancer before age 50 or ≥1 F/SDR with breast cancer before age 50 and ≥1 F/SDR with ovarian cancer at any age.

TABLE 3

Odds ratios (OR) and 95% confidence intervals (CI) for the association between timing of CRRM (pre- vs post-GCRA) and presence of an indication

	Pre-GCRA CRRM (*n* = 57)	Post-GCRA CRRM (*n* = 45)	OR[a] (95% CI)	*P* value
Indications				
No	18	4	1	
Yes	39	41	5.3 (1.6–17.8)	.007

[a] Age at diagnosis was included in the logistic regression model.

GCRA, genetic cancer risk assessment; CRRM, contralateral risk-reducing mastectomy.

TABLE 4

Odds ratios (OR) and 95% confidence intervals (CI) for the association between time period of diagnosis (before or after January1997) and the choice of pre-GCRA CRRM

	Diagnosed prior to Jan 1997 (*n* = 131)	Diagnosed in or after Jan 1997 (*n* = 247)	OR[a] (95% CI)	*P* value
Pre-GCRA CRRM				
Yes	32	25	1	
No	99	222	2.9 (1.6–5.2)	.0003

[a] Age at diagnosis was included in the logistic regression model.

GCRA, genetic cancer risk assessment; CRRM, contralateral risk-reducing mastectomy.