Minireview

Utilization of Screening and Preventive Surgery Among Unaffected Carriers of a BRCA1 or BRCA2 Gene Mutation

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Abstract
Objective: Women who are carriers of BRCA gene mutations have an elevated lifetime risk of developing breast or ovarian cancer. Although a number of risk-reducing options are currently available to mutation carriers, uncertainty exists in terms of their efficacy. A systematic review of the literature was conducted to describe the utilization of screening and preventive surgery among unaffected mutation carriers in the face of uncertainty.

Methods: MEDLINE, PubMed, and CANCERLIT, English-only computerized literature searches were done to identify articles pertaining to decisions made by unaffected BRCA mutation carriers to reduce risk of breast and ovarian cancer. Studies were required to include information on choices taken by at-risk women following disclosure of a positive BRCA test.

Results: Only seven studies (5 American and 2 Dutch studies) were identified. The proportion of mutation carriers who chose preventive surgery over screening varied widely across the studies, ranging from 0% to 54% for prophylactic mastectomy and from 13% to 53% for prophylactic oophorectomy. Furthermore, a significant minority of women who chose surveillance failed to comply with the recommended schedule.

Conclusion: There is considerable variability within and between countries in risk reduction strategies utilized by healthy mutation carriers. This variability may relate to differences in (1) population characteristics; (2) recommendations for follow-up care of unaffected carriers; (3) prevailing values towards body integrity, femininity, and preventive surgery; and (4) health care funding systems. Future research needs to provide further insight into factors influencing women's decisions to adopt various risk reduction strategies.

Introduction
Family history has long been recognized as a major risk factor for breast and ovarian cancers. In the mid-1990s, mutations in two identified breast cancer genes, BRCA1 and BRCA2, were isolated. In the general population, ~0.1% to 0.2% are carriers of BRCA1 or BRCA2 mutations, with specific subgroups of the population, for instance the Ashkenazi Jewish population having an increased prevalence of carriers (1, 2).

The BRCA1 and BRCA2 gene mutations are highly penetrant, although estimates vary as to the lifetime risk of carriers. Kauff et al. (3) estimates that for a female mutation carrier, the risk of developing breast cancer by age 70 is between 60% and 85%, and the risk of developing ovarian cancer by age 70 is between 15% and 65%. Hereditary breast and ovarian cancer is more likely to strike at a younger age than sporadic cancer, and in some carriers bilateral breast cancer or both breast and ovarian cancer develop (4, 5).

For healthy or unaffected women from hereditary breast and ovarian cancer families, genetic testing for BRCA mutations offers the opportunity to choose risk reduction strategies based on a more precise estimate of individual risk than has been available in the past. In terms of breast cancer, the most widely recommended strategy entails frequent, intense surveillance that combines annual mammography, annual or semiannual clinician breast examination, and monthly breast self-examination, beginning at age 25 to 35 years (6, 7). Whereas heightened surveillance cannot prevent the development of breast cancer, it increases the likelihood of early detection and effective treatment. The sensitivity of mammograms, however, has been shown to be lower among younger women, and for BRCA mutation carriers the risk for early-onset breast cancer is increased up to 20-fold (2, 5, 8). It has been estimated by Meijers-Heijboer et al. (9) that ~25% of young, high-risk women that undergo close surveillance will develop breast cancer and eventually die from the disease. Moreover, there are concerns that women may not comply with the schedule of regular examinations (7) or that the radiation incurred by mammography may slightly increase the risk of breast cancer in healthy BRCA mutation carriers, who by the nature of the mutations have defective DNA repair mechanisms (4, 6).
Alternate, but more aggressive and controversial, risk reduction strategies include chemoprevention with tamoxifen and prophylactic bilateral mastectomy (PM; ref. 7). There is, however, limited evidence regarding the efficacy of both strategies. A small study by King et al. (10) found that tamoxifen reduced, albeit insignificantly, the incidence of breast cancer in BRCA2 mutation carriers by 62% but had no effect for BRCA1 mutation carriers. Furthermore, the utilization of chemoprevention by healthy carriers is unknown. In terms of PM, a retrospective study by Hartmann et al. (11) showed that PM significantly reduced risk of breast cancer by at least 90% among 639 women with moderate or high risk of breast cancer. More recently, Meijers-Heijboer et al. (12) found that over 3 years of follow-up, none of 76 BRCA mutation carriers who underwent a PM developed invasive breast cancer, whereas 8 of 63 carriers who chose surveillance did. There are, however, significant risks associated with PM, including disfigurement, surgical complications, severe emotional trauma following surgery and breast reconstruction, and difficulties with body image and intimacy (13). Furthermore, Sakaforas (7) notes that there have been documented cases where breast cancer developed in the remaining breast tissue.

The recommended risk reduction options for ovarian cancer also include close surveillance and preventative surgery. However, the unreliability of current screening methods (annual or semiannual serum CA-125 levels and transvaginal ultrasounds), in conjunction with the lethality of advanced ovarian cancer has led experts to recommend bilateral prophylactic oophorectomy (PO) after completion of childbearing (6). Most recently, two studies have provided data supporting the efficacy of PO for reducing not only the risk of ovarian cancer among carriers but also the risk of breast cancer (3, 14). Despite the potential benefits of PO, there are medical and psychological risks that must be considered, including surgical complications, occurrence of postoopherectomy epithelial cancer, elevated risk of both osteoporosis and cardiovascular disease due to estrogen deprivation, and physical symptoms of menopause that may negatively impact on quality of life (15).

It is clear that considerable uncertainty surrounds the efficacy of current surveillance and preventative strategies recommended for healthy women with cancer-predisposing BRCA mutations. There are also concerns about the risks associated with prophylactic surgery as well as the profound effect that surgery may have on body image, intimacy, and lifestyle (7, 13, 15). We therefore conducted a systematic review of the literature to describe the utilization of screening and prophylactic surgery among mutation carriers in the face of this uncertainty. The intent of this review is to provide information that may inform both genetic counseling and medical care of women at risk for development of hereditary breast and ovarian cancer.

Materials and Methods

Using MEDLINE, PubMed, and CANCERLIT, computerized, English-only literature searches were done to identify all published literature concerning choices made by healthy female carriers of BRCA1 and BRCA2 mutations in terms of risk reduction. The search strategy for articles between 1996 and 2003 included in various combinations the following terms: prophylactic, oophorectomy, mastectomy, surgery, decision, attitude, choices, presymptomatic, BRCA1 and BRCA2, genetic, mammogram, chemotherapy, breast cancer, ovarian cancer, and prevention. To be included in this review, studies were required to include information on breast (ovarian) cancer risk reduction decisions made by healthy, presymptomatic women who knew their mutation status and who had no prior history of breast (ovarian) cancer. Studies that ascertained medium or high-risk women based solely on family history (16) and studies that investigated either the efficacy or utilization of only one risk reduction option (e.g., mammography only or PM only) were excluded (17-19). All available abstracts were reviewed and the full text of an article was consulted where eligibility was unclear. Bibliographies of both eligible and closely related articles were searched for other potentially eligible articles.

Results

The systematic review of the literature identified seven studies that met the inclusion criteria (2, 3, 9, 13, 20-22). Five of the seven studies examined actions taken by women to reduce breast cancer risk after disclosure of a positive BRCA test (2, 9, 13, 20, 21). In all five, women were counseled to undergo either PM or frequent surveillance to reduce breast cancer risk. Only one study (2) offered chemoprevention with tamoxifen and raloxifene, and even then only to postmenopausal women. All seven studies examined actions taken to reduce ovarian cancer risk. In all cases, women were counseled to undergo either PM or frequent surveillance. We chose to exclude one of the studies that looked at options to reduce risk of ovarian cancer (3) because 86% of mutation carriers recruited for this study had participated in a previous study (2).

Risk Reduction for Breast Cancer. Table 1 shows selected characteristics of the five studies that investigated the risk reduction strategies taken by healthy mutation carriers. The studies recruited women who were involved in ongoing genetic research protocols (2) or who were members of families known to carry a BRCA mutation (9, 13, 20, 21). Two studies were conducted in the Netherlands and three in the United States. The study population for both Dutch studies consisted entirely of women who came from families known to carry a BRCA1 or BRCA2 mutation and who had a first-degree relative affected by breast or ovarian cancer (i.e., women with a pretest risk of 50% for the mutation). By contrast, some women in the American studies were not from BRCA1-linked families (2), whereas others were from either a BRCA1-linked extended kindred (20) or BRCA1- or BRCA2-linked families (21). Furthermore, American women may or may not have had first- or second-degree relatives with breast or ovarian cancer. As shown, there was considerable diversity across the five studies in terms of sample size. The largest study ascertained 194 mutation carriers, whereas the smallest study enrolled 26. There was also considerable diversity both within and between studies regarding duration of follow-up from the date of receiving BRCA test results. Four studies, however, provided data on risk reduction strategies that were adopted in the 12 months after the
With one exception (2), the studies did not report the age distribution of mutation carriers. However, participants in all five studies were 25 years or older to ensure their eligibility for both surveillance and PM. Self-reports of utilization of either surveillance or preventative surgery was confirmed through medical records in two studies only (2, 9).

Table 1 also indicates that the proportion of healthy mutation carriers who obtained a PM varies considerably across the five studies and ranges from 0% to 54% in the 12 months following a positive test result. The largest study (2) found that 14.9% of women chose PM. Note that the two studies reporting the highest utilization of PM (51% and 54%) were both conducted in the Netherlands.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Location of study</th>
<th>Sample size of healthy mutation carriers</th>
<th>Method used to assess outcome</th>
<th>Follow-up period</th>
<th>Choice of risk reduction strategy</th>
</tr>
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<tbody>
<tr>
<td>Botkin et al. (20)</td>
<td>Females from an extended kindred known to carry a single BRCA1 mutation, recruited between 1995 and 1997, predominantly Mormons.</td>
<td>Salt Lake City, UT, USA</td>
<td>37</td>
<td>In-person interview</td>
<td>12 months</td>
<td>100% (37) 0% (0)</td>
</tr>
<tr>
<td>Lerman et al. (21)</td>
<td>Females from an extended BRCA1- or BRCA2-linked families, enrolled in research protocol from July 1994 to October 1997</td>
<td>Omaha, NE, USA</td>
<td>29</td>
<td>Telephone interview</td>
<td>12 months</td>
<td>97% (28) 3% (1)</td>
</tr>
<tr>
<td>Lodder et al. (13)</td>
<td>Females from families known to carry a BRCA1 or BRCA2 mutation and with a first-degree relative with breast or ovarian cancer, who underwent genetic testing, Department of Clinical Genetics, Erasmus University, from December 1995 to April 1998</td>
<td>Rotterdam, the Netherlands</td>
<td>26</td>
<td>In-person interview</td>
<td>12 months</td>
<td>46% (12) 54% (14)</td>
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<tr>
<td>Meijers-Heijboer et al. (9)</td>
<td>Females from families known to carry a BRCA1 or BRCA2 mutation, and with a first-degree relative with breast cancer or ovarian, who were seen at the Family Cancer Clinic and underwent BRCA1/2 testing, Department of Clinical Genetics, Erasmus University, from Jan 1, 1994 to Jan 1, 1998</td>
<td>Rotterdam, the Netherlands</td>
<td>68</td>
<td>Clinical records</td>
<td>12 months</td>
<td>53% (36) 47% (32) 51% (35)</td>
</tr>
<tr>
<td>Scheuer et al. (2)</td>
<td>Females who enrolled in one of three follow-up studies (one for those of Ashkenazi origin) and received genetic testing at Memorial Sloan-Kettering Cancer Center, from June 1, 1995 to October 31, 2000</td>
<td>New York, NY, USA</td>
<td>194</td>
<td>Telephone interview plus clinical records and pathology reports</td>
<td>Mean = 24.1 months; range = 1.6-66.0</td>
<td>85% (165) 15% (29)</td>
</tr>
</tbody>
</table>

*Prophylactic mastectomy (PM).
Three studies (2, 9, 13) compared women who chose PM with those who chose surveillance on age and parental status. Women who chose PM were younger (2, 9, 13) and more likely to have children (9, 13). In the study by Meijers-Heijboer et al. (9), younger age and parenthood jointly predicted 70% of PMs obtained in women ages ≤50 years. In addition, a woman’s prior exposure to cancer in her family was shown to influence choice. Women choosing PM had a greater number of first- or second-degree relatives with breast or ovarian cancers than women choosing surveillance (2, 13) and were on the average younger when first confronted with breast or ovarian cancer in the family (13).

As noted earlier, a potential problem for the surveillance option is poor compliance. Three studies provided information on adherence to surveillance recommendations by healthy carriers (2, 20, 21). One study reported a significant increase in surveillance after genetic testing, with over 90% of carriers who selected this option complying with both mammogram and clinical breast examination recommendations (2). The second study also reported a significant increase in the utilization of annual mammography after testing (20). In the 12 months before testing, 22% of the carriers had obtained a mammogram compared with 62% and 57% at 1 and 2 years post-testing, respectively. By 2 years post-testing, however, 29% of carriers had failed to obtain a single mammogram. In addition, the uptake of annual mammograms was considerably lower in carriers between the ages of 25 and 39 years (45% and 35% at 1 and 2 years post-testing, respectively) compared with those ≥40 years (82% at both 1 and 2 years post-testing). The third study (21) found no increase in mammogram use at 1 year after testing, with 68% of carriers reporting an annual mammogram. Again, younger carriers had a lower utilization of mammography than carriers ages >40 years.

Risk Reduction for Ovarian Cancer. Table 2 presents the results of the six studies that provided data on decisions taken to reduce ovarian cancer risk, either by surveillance or by PO. The utilization of PO was higher than that of PM, ranging from 13% to 53% in the 12 months after receipt of test result. Differences in age distribution of participants across the studies may partially account for the observed variability. As shown by Botkin et al. (20; Table 2), utilization of PO was associated with older age. The two studies with the lowest PO uptake reported on carriers ages ≥25 years, whereas the remaining studies reported on women ages ≥35 years. Schwartz et al. (22) reported that family history of ovarian cancer and perceived ovarian cancer risk were also associated with the uptake of PO. Adherence to ovarian cancer screening guidelines was relatively low (≤43%) in three studies (20-22), although one of these studies reported a significant increase in screening compared with the year before genetic testing. One study reported higher compliance (74%; ref. 2).

Discussion

In the literature, there are limited data on strategies utilized by healthy BRCA1 or BRCA2 mutation carriers to reduce their risk of breast and ovarian cancer. Furthermore, the existing studies have described the utilization of surveillance and prophylactic surgery only. To the best of our knowledge, no study has looked at the utilization of chemoprevention.

The proportion of healthy carriers who choose preventative surgery versus surveillance varied considerably across the studies. For instance, the utilization of PM to prevent breast cancer ranged from 0% to 54% in the 12 months after the disclosure of a positive BRCA test. Although differences in sample size may explain some of the observed variability across studies, a more plausible explanation is study location. Three studies were conducted in the United States, where no recommendations have yet been made for or against PM, whereas the remaining two studies were conducted in the Netherlands, where PM has been recommended for proven BRCA1 and BRCA2 mutation carriers since 1997. There are also important differences between the two countries in terms of health care reimbursement. In the Netherlands, prophylactic surgery is fully or partially covered by public health insurance (9). This contrasts with the United States where prophylactic surgery is mainly covered by private health insurance and thus is likely unaffordable for some American women. In addition, cultural differences may exist in terms of values and attitudes towards body integrity, femininity, and preventive surgery (23). Bouchard et al. (24) have also shown that there are international differences in the way cancer geneticists deal with BRCA testing and chemoprevention and prophylactic surgery. Together, these differences could account for the substantially higher proportion of PM reported by the Dutch studies compared with the American studies. Moreover, there may be important sociodemographic differences between the mutation carriers in the Dutch studies and those in the American studies. It has been shown that women who choose PM tend to be younger (2, 9, 13), to have children (9, 13), and to report a greater number of breast and ovarian cancer among family members (2, 13). Unfortunately, there are insufficient data to determine whether the study populations differed significantly in terms of age, parental status, and number of affected relatives. Although the Dutch studies recruited only women who came from families known to carry a BRCA mutation and who had a first-degree relative affected by breast or ovarian cancer, this does not mean that Dutch women had more relatives affected by breast or ovarian cancer than American women. Similar to PM, the utilization of PO varied widely across the studies, ranging from 13% to 53% in the 12 months following the receipt of test results. Again, the Dutch studies reported the highest rates. However, there was considerable variability in utilization of PO across the four American studies, possibly due to differences in population characteristics, such as age, completion of childbearing, and socioeconomic status. Botkin et al. (20) showed that the utilization of PO was substantially higher in carriers over the age of 40 compared with those between the ages of 25 and 39 (78% versus 29%). Only 27% of carriers underwent PO in the study conducted by Schwartz et al. (22), who argued that the relatively low uptake of PO compared with that reported by other studies (3, 9) might reflect constrained financial resources. Women in this sample received free genetic counseling and testing. Another
Table 2. Characteristics of six studies that investigated strategies taken by healthy BRCA1 or BRCA2 mutation carriers to reduce risk of ovarian cancer

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<td>12 months</td>
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<td>Rotterdam, the Netherlands</td>
<td>45 Clinical records</td>
<td>12 months For entire study period (median = 21 months, range = 10.0-61.0)</td>
<td>47% (21) 36% (16)</td>
<td>53% (24) 64% (29)</td>
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<td>179 Telephone interview combined with clinical records and pathology reports</td>
<td>Mean = 24.1 months, range = 1.6-66.0</td>
<td>49% (89)</td>
<td>51% (90)</td>
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<td>Schwartz et al. (22)</td>
<td>Females from families with known BRCA1 or BRCA2 mutations who underwent free genetic testing through Lambardi Center Cancer Assessment and Risk Program from 1995 to 2000</td>
<td>Washington, DC, USA</td>
<td>79 Telephone interview</td>
<td>12 months</td>
<td>73% (58)</td>
<td>27% (21)</td>
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</tbody>
</table>

*Prophylactic Oophorectomy (PO).*

*In an updated analysis, Kauff et al. (3) reported that 42% and 58% of carriers underwent surveillance and PO, respectively.*
striking finding was the marked difference in women's utilization of PO and PM in two American studies (2, 20). This observation is consistent with previous reports of the higher acceptability of PO relative to PM (23). The higher uptake of PO may reflect several factors, for instance, (1) a heightened perceived benefit of surgery given the lethality of advanced ovarian cancer; (2) a greater uncertainty about the efficacy of screening to detect early stage ovarian cancer; and (3) a perception that PO is a less invasive procedure than PM, leading to fewer surgical complications and less disturbances to body integrity and image.

The results of this review also indicate that a minority of women who opt for close surveillance fail to comply with follow-up recommendations (2, 20-22). Adherence to annual mammography recommendations generally increased after the disclosure of a positive test result but ranged from 57% to 93%. A major predictor of mammogram use was age, with a considerably lower uptake among carriers ages 25 to 39 years. Peshkin et al. (17) reported similar findings in a sample of younger carriers who were self-referred for genetic testing. The same researchers noted that these women were obtaining clinical breast examinations as recommended and suggested that physicians following these women might not recommend annual mammography because of their young age. Income and number of relatives with breast cancer have also been found to be associated with mammogram use (25). Adherence to ovarian cancer screening was lower than that of breast cancer screening and again may reflect greater uncertainty about the efficacy of ovarian cancer screening to detect early disease. In the literature, compliance with screening recommendations has been related to number of relatives with ovarian cancer, perceived risk of ovarian cancer, and Jewish Ancestry (25). The latter factor may partially explain the relatively high adherence rates reported by Scheuer et al. (2). An unspecified portion of this study’s sample was of Jewish Ancestry.

One important limitation of this research is the select nature of the studied samples, thereby decreasing the generalizability of the findings. As indicated earlier, all studies recruited participants who were members of BRCA-linked families or who were involved in ongoing genetic research. More population- and community-based studies in this area are needed. In addition, there were differences in selection criteria across the studies (e.g., BRCA type, family history, and sociodemographic features). Based on the published data, it was difficult to determine the impact of study differences in risk profiles on the utilization of screening and preventive surgery. A third limitation relates to the fact that the majority of studies used self-report to ascertain utilization of screening or preventative surgery (26, 27). Ideally, self-reports of utilization would be verified through medical records. Finally, the study populations of the two Dutch studies (9, 13) may overlap somewhat because carriers were recruited from the same clinic. The existence of any overlap could not be determined from the published studies. Nevertheless, the observed differences in screening and preventive surgery between Dutch and American women would remain if either one of the Dutch studies was excluded from the review.

In conclusion, there is considerable variability within and between countries in risk reduction strategies utilized by healthy BRCA1 or BRCA2 mutation carriers. This variability likely reflects differences in population characteristics, in prevailing values and attitude towards body integrity, femininity, and preventive surgery, and in health care funding systems. The variability may also relate to the fact that the studies under review recruited their samples between 1994 and 2000, when follow-up recommendations for BRCA mutation carriers were evolving internationally. Future research in this area should improve our understanding of the factors that influence women’s decisions to adopt particular risk reduction strategies. This, in turn, should help both healthy mutation carriers and their clinicians decide upon the optimal strategy.

References

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