MINI REVIEW

PREVENTION OF BREAST CANCER IN WOMEN WHO CARRY BRCA1 OR BRCA2 MUTATIONS: A CRITICAL REVIEW OF THE LITERATURE

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The purpose of our study was to review the evidence for the efficacy of surveillance for early detection, bilateral prophylactic mastectomy, prophylactic oophorectomy and chemoprevention in preventing breast cancer and improving survival of BRCA1 or BRCA2 carriers. A critical review of journal articles published between 1998 and 2004 identified by searches of MEDLINE, PubMed and references of retrieved articles was undertaken. None of the current evidence is based on randomized studies. The efficacy of surveillance for early detection of breast cancer among BRCA1 or BRCA2 carriers is not yet established. Screening with clinical breast examination and mammography showed lower sensitivity in BRCA1 or BRCA2 carriers than in the general population. Screening with MRI might offer higher sensitivity rates than mammography. Prophylactic mastectomy was shown to significantly reduce the risk of breast cancer by 89.5–100%. However, of all strategies reviewed, mastectomy was the least acceptable to women at high risk. Tamoxifen use was associated with breast cancer prevention among BRCA2 carriers (RR=0.38, 95%CI: 0.06–1.56), in BRCA1 or BRCA2 carriers with breast cancer, tamoxifen use was associated with the prevention of secondary breast cancer (OR=0.50, 95% CI: 0.28–0.89). Prophylactic oophorectomy was associated with hazard ratios for breast cancer of 0.47 (95%CI:0.29 – 0.77) and 0.32 (95%CI: 0.08 –1.20), in retrospective and short follow-up prospective cohort studies, respectively. There is a pressing need for more studies in order to determine which of the 4 strategies alone, or in combination, is the most effective for the prevention of breast cancer and for the improvement of survival of BRCA mutation carriers.

Key words: BRCA1 or BRCA2; prophylactic mastectomy; prophylactic oophorectomy; chemoprevention; surveillance

Approximately 7% of breast cancer cases are estimated to be due to breast cancer susceptibility genes.6 In the last decade, 2 such susceptibility genes, BRCA1 and BRCA2, were identified on the long arms of chromosomes 17 and 13, respectively. The highest population prevalence rates of BRCA1 and BRCA2 were described among Ashkenazi Jews at about 2.5%;2–4 these mutations include BRCA1 or BRCA2 carriers, the prevalence is 10.4%,10 while among family history of breast cancer.6–9 Among unselected Icelandic breast cancer patients, the overall prevalence is 0.13%, 1.09% and 1.52%, respectively.2 In 5382insC and 185delAG in BRCA1, population prevalence rates of 0.1% and 0.02% were reported for the general population.8,9 In BRCA2 carriers with breast cancer, tamoxifen use was associated with the prevention of secondary breast cancer (OR=0.50, 95% CI: 0.28–0.89). Prophylactic oophorectomy was associated with hazard ratios for breast cancer of 0.47 (95%CI:0.29 – 0.77) and 0.32 (95%CI: 0.08 –1.20), in retrospective and short follow-up prospective cohort studies, respectively. There is a pressing need for more studies in order to determine which of the 4 strategies alone, or in combination, is the most effective for the prevention of breast cancer and for the improvement of survival of BRCA mutation carriers.

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The estimated cumulative lifetime risk of breast cancer for women who carry mutations in BRCA1 or BRCA2 ranges from as high as 80%14,15 to less than 60%.16 In a meta-analysis of 22 studies, among first-degree relatives of 500 index patients with BRCA mutations, the average lifetime cumulative risks for breast cancer were 65% (95% CI: 44–78%) and 45% (31–56%) in BRCA1 and BRCA2 mutation carriers, respectively. There was evidence for variation in risk by mutation position for both genes.17 Much higher estimates were reported in the recently published New York Breast Cancer Study (NYBCS), where the lifetime risk of breast cancer was estimated in relatives of Ashkenazi Jewish probands with breast cancer who were confirmed mutation carriers. This study demonstrated a lifetime risk of developing breast cancer of 82% among BRCA mutation carriers from low and high incidence families.18 Both the NYBCS and the meta-analysis found a reduced lifetime risk in women from earlier birth cohorts.

The NYBCS also found delayed development of breast cancer among carriers who exercised in adolescence and who had normal weight at menarche and at age 21, suggesting a gene-environment interaction.18,19

It is not yet clear whether other recognized risk factors for breast cancer, such as reproductive and hormonal factors, operate in the same way in women who carry a mutation in the BRCA1 or BRCA2 genes20 as in noncarriers, and there is little evidence that oral contraceptives increase the risk of breast cancer among BRCA1 mutation carriers.21 Breast neoplasms in carriers of BRCA1 and BRCA2 mutations have been found to be, on average, of a higher overall grade than in noncarriers.22,23 In BRCA1 mutation carriers, they are also characterized by a larger size at diagnosis, a higher rate of grade 3 histoprotostatic factors and a higher frequency of estrogen- and progesterone-receptor negativity, compared to sporadic tumors in age-matched controls.23–25 These tumors also exhibited more pleomorphism, a higher mitotic count and less tubule formation than those in controls, whereas cancers in BRCA2 mutation carriers exhibited less tubule formation but no difference in pleomorphism or mitotic count, compared to those among noncarriers.22 While the occurrence of invasive lobular carcinoma and invasive ductal carcinoma was not significantly different between carriers of BRCA1 or BRCA2 mutations and controls, carriers of BRCA1 mutations showed less ductal carcinoma in situ around the invasive lesion than controls.22

These findings suggest that breast cancer due to BRCA1, would have a different natural history compared to sporadic disease. Some studies have indeed demonstrated a poorer prognosis in BRCA1 carriers with breast cancer compared to non carriers,23,26 possibly attributed to known prognostic factors.26 However, other studies have not confirmed this finding.25,27

Currently, a BRCA1 or 2 carrier has 4 alternatives for the medical and surgical prevention (either primary or secondary) of breast cancer: prophylactic mastectomy, prophylactic oophorectomy, chemoprevention and surveillance.

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breast cancer. These include surveillance for the early detection of breast cancer (by mammography, clinical breast examination, self-examination of the breast, ultrasound and/or MRI), bilateral prophylactic mastectomy, prophylactic oophorectomy and chemoprevention. The aim of our report is to review the current state of knowledge regarding the efficacy of these strategies in preventing the development of breast cancer and improving survival of women who carry BRCA1 or BRCA2 mutations.

METHODS

Data for this review were identified by searches of MEDLINE, PubMed, and references from relevant articles using the search terms “BRCA1”, “BRCA2”, with “prevention”, “breast cancer”, “prophylactic mastectomy”, “prophylactic oophorectomy”, “tamoxifen”, “chemoprevention”, “screening”, “mammography” and “MRI”. Only articles in English were reviewed. We included studies from 1998 to 2004.

RESULTS

Table I presents a summary of all primary studies that assessed the efficacy of 1 or a combination of these strategies.

**Surveillance**

The recommendations of the “Cancer Genetics Studies Consortium for Surveillance of Women at High Risk for the Development of Breast Cancer” include semi-annual breast examination and annual mammography beginning between the age of 25 and 35 years for carriers. However, these recommendations are based on expert opinion and there is little evidence that routine surveillance reduces cancer mortality in BRCA1 or BRCA2 carriers.

Brekkelmans et al. followed 1,198 women at high risk for the development of breast cancer. The program included monthly self-examination of the breast, semi-annual clinical breast examination and yearly mammography. Since 1995, MRI of the breast was optional for women with dense breast tissue and/or BRCA mutation. A total of 35 breast malignancies were diagnosed, 31 of which were invasive carcinomas. Twenty-six breast malignancies were discovered as a result of the screening examinations: 9 by mammography, 3 by MRI (which was not performed in all women), 12 by clinical examination and mammography and 1 by clinical examination only. The overall sensitivity of the screening program was 74%, and a trend for increasing sensitivity with age was seen. Among the 118 BRCA1 or BRCA2 carriers, 9 cases of breast cancer were diagnosed, of which 5 were diagnosed in the screening program, yielding a surveillance sensitivity of 50%. Thus, although the numbers were too small in order to draw meaningful conclusions, the study suggests that screening examinations may be less effective in BRCA1 or BRCA2 carriers than in other high-risk women.

Similar surveillance sensitivity was shown in the study by Scheuer et al., where 165 male and female carriers of BRCA mutations were advised to take part in a program that included semi-annual mammography, monthly breast self-examination and clinical examination 2 to 4 times a year. During a mean follow-up of 24.8 months, breast cancer was diagnosed in 12 women; 6 tumors were detected by radiographic surveillance and 6 were interval cancers, yielding a surveillance sensitivity of 50%. The lower sensitivity of mammography in BRCA mutation carriers might be a result of higher breast density in women with family history.

Tilanus-Linthorst et al. suggested that the morphological features of tumors that emerge in BRCA carriers are such that they decrease the probability of detection by mammography (i.e., less spiculated masses due to lack of tumor-surrounding fibrosis).

There is growing evidence that MRI may offer better sensitivity than mammography for the early detection of breast cancer in BRCA1 or BRCA2 carriers. In a nonrandomized trial by Kuhl et al., 192 women, aged 18–65 years, who were at a very high risk for the development of breast cancer according to family history,
## TABLE IB – THE EFFICACY OF PREVENTIVE STRATEGIES FOR REDUCING BREAST CANCER IN BRCA1 OR BRCA2 CARRIERS

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Reference</th>
<th>No. of carriers included</th>
<th>Mean follow-up</th>
<th>Relative risk reduction percent (1 – RR)*100 (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic mastectomy</td>
<td>Hartmann (38, 39)</td>
<td>26</td>
<td>14 years</td>
<td>89.5–100 (41.4–100)</td>
<td>The observed breast cancer cases were compared to an expected number according to penetrance models</td>
</tr>
<tr>
<td></td>
<td>Meijers-Heijboer (40)</td>
<td>139</td>
<td>3 years</td>
<td>100 (−64–100)</td>
<td>The observed breast cancer cases were compared to an expected number according to penetrance models</td>
</tr>
<tr>
<td></td>
<td>Rebbeck (41)</td>
<td>480</td>
<td>6 years</td>
<td>Analysis 1&amp;2: 91–95 (99–62) Analysis 3&amp;4 (prophylactic surgery before center ascertainment excluded): 100 (NA)</td>
<td>Breast cancer incidence was compared between prophylactic surgery cases and mutation matched controls</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>King (48)</td>
<td>19</td>
<td>47.7 months</td>
<td>BRCA1: −67 (−970–69)</td>
<td>Case-control study. secondary breast cancer prevention</td>
</tr>
<tr>
<td></td>
<td>Narod (49)</td>
<td>NA</td>
<td></td>
<td>BRCA1: 62% (26–81%) BRCA2: 37% (−50–80%)</td>
<td>Breast cancer patients who underwent prophylactic oophorectomy were significantly older at diagnosis than controls (52.5 vs 46.7; (p = 0.03))</td>
</tr>
<tr>
<td></td>
<td>Rebbeck (44)</td>
<td>241 (99 prophylactic oophorectomy 142 controls)</td>
<td>PO: 10.7 years Control: 11.9 years</td>
<td>53 (23–71)</td>
<td>Surveillance included instructions for annual mammography, clinical examination of the breast 2–4 times a year and monthly self-examination</td>
</tr>
<tr>
<td></td>
<td>Kauff (45)</td>
<td>170 (98 oophorectomy, 72 surveillance)</td>
<td>23.4 months</td>
<td>68 (−20–92)</td>
<td>Secondary breast cancer prevention</td>
</tr>
<tr>
<td></td>
<td>Narod (49)</td>
<td>NA</td>
<td></td>
<td>58 (17–78)</td>
<td>Estimate was adjusted for other treatments, ethnic group, parity, and smoking habits</td>
</tr>
<tr>
<td></td>
<td>Narod (49)</td>
<td>NA</td>
<td></td>
<td>84 (31–96)</td>
<td>Odds ratio for the comparison of treatment with oophorectomy and tamoxifen vs. neither oophorectomy nor tamoxifen</td>
</tr>
</tbody>
</table>

1Sen, sensitivity–2Sp, specificity–3PPV, positive predictive value–4NPV, negative predictive value.
were screened for breast cancer. The study population included 35 BRCA carriers. The screening protocol included annual mammography and MRI, and biannual high frequency ultrasound examinations. Among the 117 patients younger than 40 years of age, annual mammography was recommended by the radiologist only to those whose breast density on the first mammogram allowed a reasonable reading. In the first screening round, 6 cancers were detected. In the second screening round, 3 of 101 asymptomatic women had breast cancer. All screened tumors corresponded to pTis-pT1 stage. Of the 9 breast cancer patients, 6 had BRCA1 and 1 had a BRCA2 mutation. For the other 2, mutation status was unknown. The sensitivities of MRI, mammography and ultrasound were 100%, 88% and 33%, respectively. Combining the results of ultrasound with mammography, 4 out of 9 malignancies were detected, reaching a sensitivity of 44%. The specificity of MRI was 95%, compared to 93% and 80% for mammography and ultrasound, respectively. The positive predictive value (PPV) of MRI was 64%, while mammography and ultrasound had PPV of 94% and 93%, respectively. The negative predictive values (NPV) were 95%, 88% and 76% for MRI, mammography and ultrasound, respectively.

Warner et al. studied 196 women at high risk for the development of breast cancer (96 BRCA mutation carriers, 24 women with strong family histories) who underwent mammography, ultrasound, MRI and clinical breast examination. Breast biopsy was performed whenever one of these investigations raised the suspicion of tumor. A total of 33 patients underwent a biopsy, yielding 6 invasive cancers and 1 ductal carcinoma in situ (DCIS). All 6 tumors were detectable by MRI. In contrast, 3 were detected by ultrasound, 2 by mammography and 2 by clinical examination. Since there was no follow-up and there is no information as to how many tumors were missed, the sensitivity of these measures cannot be estimated, although these preliminary results suggest that all examinations MRI probably has the highest sensitivity. On the other hand, the PPV of MRI and mammography were 26% and 66%, respectively. Thus, more unnecessary biopsies would be performed based on MRI results compared to mammography.

Stoutjesdijk et al. conducted a retrospective cohort study of 179 women with an increased familial risk of breast cancer (calculated lifetime risk greater than 15%), including at least 25 BRCA mutation carriers. Over 2 years of follow-up, 40 women had mammography only, 49 underwent MRI as a single modality, 15 underwent both mammography and MRI in different years and 75 had both examinations within 4 months, 15 of whom were mutation carriers. These 75 women most probably had 1 of the modalities as a diagnostic test rather than a screening test. Findings on both MRI and mammograms were classified according to the Breast Imaging-Reporting and Data Systems (BI-RADS) score, in which scores 3, 4 and 5 grade imaging results as probably benign, suspicious abnormality and highly suggestive of malignancy, respectively.

A total of 13 tumors were detected, of which 12 were detected in the group that underwent both MRI and mammography within 4 months. No interval tumors were diagnosed. Of the 258 MRI examinations, 30 were scored BI-RADS 3–5, 13 proved to be malignant, yielding a sensitivity of 100%, specificity of 93%, PPV of 43% and NPV of 100%. Of the 262 mammograms, 15 were assigned BI-RADS score of 3–5, 5 of which were proved malignant and 7 were false negative reports, yielding sensitivity of 42%, specificity of 96%, PPV of 33% and NPV of 97%. When the cut-off point was set at BI-RADS 4, the specificity, sensitivity, PPV and NPV were 92%, 98%, 71% and 99.6% for MRI, and 42%, 99%, 63% and 97% for mammography. The analysis was neither stratified nor adjusted for the different risk categories of the study population. ROC curves showed significantly higher area under the curves (AUC) for MRI (0.98–0.99) compared to mammography (0.70–0.74).

Breast screening with MRI in women with a high-risk family history was also studied by Tilanus-Linthorst et al. In their study, MRI screening was performed in women with a calculated lifetime risk of breast cancer exceeding 25% who had radiologic evidence of dense fibroglandular tissue of more than 50% of the breast area as assessed by mammography. The gold standard for validation of MRI screening was the diagnosis of breast cancer within 1 year of MRI examination. Altogether, 109 women had at least 1 MRI examination, of whom 12 had a known BRCA mutation. MRI detected breast cancer in 3 women, which was not seen on mammography performed soon afterwards. Breast MRI was falsely positive in 6 women. There were no false negative MRI results. None of the 3 breast cancer patients was known to carry a BRCA mutation. According to this study, the extra cost of breast MRI in addition to mammography and physical examination was 13,930 Euro per detected cancer, about 4,930 Euro more than the cost of detecting cancer in the Dutch national screening program.

Critical appraisal

None of the studies that have investigated screening among BRCA mutation carriers have addressed the efficacy or effectiveness of screening methods in terms of outcome, such as breast cancer mortality, breast cancer stage and grade, or quality of life of breast cancer patients. Instead, these studies discussed the internal validity of either a screening protocol or specific screening modalities, mainly, MRI. These studies substantially differed in their study populations and their choice of a gold standard (necessary for the calculation of sensitivity and specificity). Most studies did not distinguish whether tests were performed as screening tests in apparently healthy women or were part of a diagnostic work-up in suspected breast cancer patients.

There is a need for more high quality evidence on the efficacy of MRI in the surveillance of breast cancer among BRCA mutation carriers. If indeed the sensitivity of MRI proves to be about 100% in detecting occult breast cancer, clear criteria should be defined as to who should receive MRI screening in order to increase its PPV, reduce unnecessary procedures and control costs.

Recently, the American Cancer Society published updated guidelines for breast cancer screening. While there were no definite recommendations for women at high risk for breast cancer, due to lack of information, the most explicit recommendation was shared decision making about screening modalities by the woman and her doctor, following a review of the current state of knowledge.

Prophylactic mastectomy

Studies of prophylactic mastectomy for the primary prevention of breast cancer have been exclusively observational and have included women who voluntarily underwent the procedure. In a historical cohort study by Hartmann et al., 639 women who had a family history of breast cancer and who had prophylactic mastectomy between the years 1960 and 1993 were followed. According to their family history, participants were defined as being at high risk (n=214) or moderate risk (n=425) for the development of breast cancer. Among the moderate risk group, 37.5 cases of breast cancer were expected, while only 4 were observed, yielding a risk reduction of 89.5%. Thirty to 53 cases of breast cancer were expected among the high risk group, while only 3 were observed, yielding a risk reduction of 90–94.3%.

Following this study, risk reduction in women known to be BRCA1 or BRCA2 mutation carriers was estimated in the same cohort. Among the 214 women who were considered at high risk and who had prophylactic mastectomy, 26 were shown to be carriers of BRCA1 or BRCA2 gene mutations, 18 of which were of clinically known importance. Two of the 3 high-risk women who developed breast cancer were BRCA negative (1 was tested and the other was considered negative according to her mother’s results). Since the mutation status of the third woman was not known, estimation of the risk reduction was made with and without the assumption that she was a mutation carrier. The efficacy of mastectomy was calculated twice according to a high and moderate
prophylactic mastectomy was performed in 76 women and mutation carriers were followed for a mean of 2.9 years. Prophylactic mastectomy was performed in 76 women and the remaining 63 had only conservative follow-up. The expected number of breast cancer cases was calculated according to literature concerning BRCA1 mutation carriers. Among the conservative follow-up group, 8 cases were observed and 6.7 cases of breast cancer were expected, yielding a nonsignificant standardized incidence ratio (SIR) of 1.2. In the prophylactic mastectomy group, no case of breast cancer was observed; thus, the hazard ratio (HR) reached zero (95% CI: 0–0.36, p=0.003). The majority of the mastectomy group (58%) had undergone oophorectomy as well.

A very recent study,43 conducted in 11 medical centers in North-America, UK and the Netherlands, evaluated the efficacy of prophylactic mastectomy in the prevention of breast cancer. BRCA1 mutation carriers who had undergone bilateral mastectomy (n=105) and mutation-, age- and center-matched controls (n=384) were followed for a mean of about 6 years from date of prophylactic surgery. Breast cancer was diagnosed in 2 women who had undergone prophylactic surgery, and in 184 women of the control group, yielding Hazard Ratio of 0.05 (95% CI: 0.01–0.22) adjusted for age and estrogen hormone exposure. After exclusion of women who had undergone prophylactic oophorectomy as well, the adjusted HR was 0.09 (95% CI: 0.02–0.38). In 2 analyses that excluded women who had undergone prophylactic surgery before center ascertainment, after a short follow-up, none of the prophylactic surgery group was diagnosed with breast cancer, as opposed to 42% and 67% of the controls (24/57 and 19/28, respectively; p values for comparing breast cancer among surgery and control groups in the 2 analyses <0.0001).

Critical appraisal

The studies of prophylactic surgery (either mastectomy or oophorectomy) include women who either chose to undergo prophylactic surgery or declined it. Therefore, no randomization was performed in these studies and the study population was self-selected. If the baseline risk for developing breast cancer were different between the surgery and nonsurgery groups, then there is a potential for selection bias by indication.42 However, if women of the surgery group have a higher risk of developing breast cancer, then the risk reduction for their risk category is merely underestimated. Different baseline risk among mastectomized and nonmastectomized women were found in the study by Scheuer et al.30 where women who underwent prophylactic mastectomy had a higher number of first and second degree relatives with breast cancer among, compared to women who declined surgery. Alternatively, women who choose to undergo prophylactic surgery might have a higher risk perception, which is not necessarily real, as suggested by Metallo et al.43. According to their analysis, women who chose prophylactic mastectomy significantly exaggerated their personal risk for breast cancer, except for BRCA1 or BRCA2 carriers who just slightly overestimated their risk for breast cancer. Other methodological issues include the exclusion of 6 women with breast cancer detected in the surgically treated breasts from the analysis in the study by Hartmann et al.40. Had these tumors occult malignancies detected because of prophylactic mastectomy, they should be at least considered in the analysis. By excluding these tumors, a detection bias might lead to the overestimation of the efficacy of mastectomy.

In the study by Meijers-Heijboer,40 as mentioned above, most of the mastectomy group had undergone oophorectomy as well. As discussed later in this review, oophorectomy itself may prevent breast cancer in BRCA1 or BRCA2 carriers. Thus, although adjustments were made for menopausal status, data were not stratified for oophorectomy status and the interaction between oophorectomy and prophylactic mastectomy was not discussed. Overall, such a bias may cause an overestimation of the risk reduction. While the strength of this study is its prospective design and its confinement to BRCA1 mutation carriers, its limitations include the short follow-up period.

While the studies of Hartmann et al.38,39 and Meijers-Heijboer et al.40 compared the observed cases of breast cancer to a calculation-based number of expected breast cancers, in the study by Rebbeck et al.41 the comparison was made between observed breast cancers among the prophylactic surgery group and the control group. Among the strengths of this study are the analyses that referred to the possible protection of prophylactic oophorectomy and to the possible risk reduction overestimation that might result from the timing of BRCA testing among women who were in the comparison group, where some had BRCA testing only after their cancer diagnosis. However, the restriction of analyses to women who had not undergone prophylactic oophorectomy and who had undergone prophylactic mastectomy after center ascertainment led to a short follow-up.

The studies by Hartmann et al.38,39, Meijers-Heijboer40 and Rebbeck et al.41 demonstrate consistent results of 85–100% relative risk reduction for the development of breast cancer among BRCA1 or BRCA2 carriers who have undergone bilateral prophylactic mastectomy.

Prophylactic oophorectomy

The incidence of breast cancer was determined in a historical cohort of 241 BRCA1 or BRCA2 carriers,42 of whom 99 women had undergone prophylactic oophorectomy and 142 were matched controls, followed on average for 10.7 and 11.9 years, respectively. None had had previous breast cancer or had undergone mastectomy. Breast cancer was diagnosed in 21 of the 99 women who had undergone prophylactic oophorectomy and in 60 women in the control group (Hazard Ratio=0.47; 95% CI: 0.29–0.77). The protective effect seemed to be strongest among women younger than 35 years when oophorectomy was performed (HR= 0.39; 95% CI: 0.15–1.04). Breast cancer was diagnosed at an older age in the prophylactic oophorectomy group compared to controls (mean age at breast cancer diagnosis: 52.5 vs. 46.7 years, respectively; p=0.03). A possible result of the difference in age at diagnosis is the longer follow-up to diagnosis in the oophorectomy group (11.4 years in the oophorectomy group and 8 years in the control group; p=0.09).

Kauf et al.45 followed 170 women found to carry a pathogenic BRCA1 or BRCA2 mutation, of whom 131 had breast tissue at risk (i.e., had not undergone previous bilateral mastectomy) for 20 months. All women were 35 years of age or older. A total of 144 women had a previous diagnosis of breast cancer. Among the 98 women who chose to undergo risk-reducing salpingo-oophorectomy, 69 had breast tissue at risk, while among the 72 who chose surveillance for ovarian cancer, 62 had breast tissue at-risk (p=0.02). During a mean follow-up of 20 months, breast cancer was diagnosed in 3 women who had salpingo-oophorectomy and in 8 women of the surveillance group. The hazard ratio for breast cancer was 0.32 (95% CI: 0.08–1.20). The hazard ratio for breast cancer or BRCA-related gynecologic cancer was 0.25 (95% CI: 0.08–0.74).

Prophylactic oophorectomy has the advantage of preventing ovarian cancer as well as breast cancer. The demonstrated efficacy of oophorectomy in BRCA1 mutation carriers is interesting, because most of BRCA1-related breast tumors are negative for estrogen receptors. It has been suggested that the hormonal blockade by oophorectomy inhibits the development of breast tumors, which may also imply a role for chemoprevention by hormonal-blockade.

Critical appraisal

As in the studies of prophylactic mastectomy, the studies of prophylactic oophorectomy include a self-selected surgery group, leading to a possible selection bias. In the study by Rebbeck et al.41 high proportions of both the prophylactic oophorectomy and the control groups were censored, but the censored proportion...
the prophylactic oophorectomy group was significantly higher than that of the control group (79% vs. 45%, respectively, \( p<0.001 \)), which might distort the results. Furthermore, significantly higher proportions of the prophylactic oophorectomy group had a history of use of oral contraceptives or hormone replacement therapy, compared to the control group, suggesting a possible modification of the risk in the prophylactic oophorectomy group by these nongenetic factors.

The study by Kauff et al.\(^45\) was a prospective cohort study. Controls were followed since genetic testing. Its limitations include a short follow-up period. Prevention of breast cancer was calculated for both primary breast cancer and secondary breast cancer, since more than 60% of the control and prophylactic oophorectomy groups had been previously diagnosed with breast cancer. There was no data on tamoxifen treatment in the 2 study groups.

Chemoprevention

The primary aim of the Breast Cancer Prevention Trial (BCPT) was to determine whether tamoxifen administered for at least 5 years prevented invasive breast cancer in healthy high-risk women.\(^47\) High risk was defined as either being 60 years of age or older, or between the ages of 35–59 years with a year predicted risk for invasive breast cancer of \( \geq 1.66\% \) according to Gail model or with a personal history of LCIS. Of the 13,388 women who participated in the trial, only 19% had 2 or more first degree relatives with breast cancer. Tamoxifen use was shown to be protective against breast cancer with risk ratio (RR) for all women of 0.51 (95%CI: 0.39 – 0.66) and was similar for women with first degree relatives with breast cancer. In this randomized controlled trial, of 288 incident breast cancer cases, only 19 were known to carry BRCA mutations (8 BRCA1 mutations and 11 BRCA2 mutations).\(^48\) Of the 8 carriers of BRCA1, 5 were treated with tamoxifen (RR = 1.67, 95%CI:0.32–10.7). Among the 11 patients who were BRCA2 carriers, 3 were treated with tamoxifen (RR = 0.38, 95%CI: 0.06 – 1.56). A higher proportion of BRCA2 patients were ER positive compared to BRCA1 patients, which might explain their benefiting from tamoxifen use. Owing to the small sample size, the study failed to reach statistical significance and it is only suggestive for the preventive role of tamoxifen in BRCA2 carriers.

The only other published study that investigated the preventive effect of tamoxifen in BRCA1 or BRCA2 carriers is a study by Narod et al.,\(^49\), where prevention of secondary breast neoplasms was estimated. This case-control study compared the history of tamoxifen intake in BRCA mutation carriers who developed bilateral breast cancer \((n=209)\) with that of BRCA carriers with unilateral disease \((n=384)\). Tamoxifen use was associated with prevention of contralateral breast cancer (OR = 0.50, 95% CI 0.28 – 0.89, adjusted for other treatments, ethnic group, parity and smoking). The protective effect of tamoxifen was greater for carriers of BRCA1 mutations \((n=476)\; \text{OR} = 0.38, 95\% \text{CI} 0.19 – 0.74) than for those with BRCA2 mutations \((n=117); \text{OR} = 0.63, 0.20 – 1.50\). The risk reduction was greatest following 2–4 years of use. An independently protective effect in the prevention of secondary breast cancer was found among carriers who had undergone prophylactic oophorectomy (adjusted OR = 0.42; 95% CI 0.22 – 0.83).

The combination of prophylactic oophorectomy with tamoxifen therapy seemed to further reduce the risk (OR = 0.16; 95% CI = 0.04 – 0.69).

Critical appraisal

The first study cited\(^48\) is an \textit{ad hoc} analysis of a randomized clinical trial. The authors assumed that randomization ensured that mutation carriers were equally distributed between the Tamoxifen and placebo treatment arms; therefore, instead of studying the breast cancer incidence ratio between tamoxifen and placebo treated BRCA mutation carriers, they calculated the ratio of breast cancer cases in each study arm. However, due to the small numbers of BRCA carriers, this assumption needs further validation.

In the study by Narod et al.,\(^49\) because mutation analysis was restricted to living women, selection bias would occur if those who had died were different from the study population in terms of exposure (tamoxifen) and/or outcome (contralateral breast cancer).

Since questionnaires were completed by cases and controls, on average, 11.8 years after initial diagnosis, information bias cannot be ruled out. It is reasonable to question whether cases (i.e., women with bilateral breast cancer) would remember treatments such as tamoxifen differently from controls. There was no reported attempt to validate the data collected by the questionnaires.

While the study by King et al.,\(^48\) suggested a preventive role of tamoxifen among BRCA2 carriers, the study by Narod et al.\(^49\) suggested preventive role for tamoxifen among both BRCA1 and BRCA2 carriers with more effective prevention among BRCA1 carriers. Chemoprevention in BRCA2 carriers seems more biologically plausible than in BRCA1 carriers, since the latter are more likely to be estrogen receptor-negative. Nevertheless, these somewhat contradictory results do not provide conclusive evidence of efficacy and underscore the need for further studies. Currently there is no information regarding the effects of raloxifene in BRCA1 or BRCA2 carriers.

DISCUSSION

The current state of knowledge suggests that prophylactic mastectomy is the most effective way to prevent breast cancer in BRCA1 or BRCA2 mutation carriers. The studies by Hartmann et al.,\(^38,39\) Meijers-Heijboers et al.,\(^40\) and Rebbeck et al.,\(^41\) demonstrated consistent results of 85–100% relative risk reduction among BRCA carriers who have undergone bilateral prophylactic mastectomy. However, the efficacy of this strategy in prolonging survival has not yet been established.

Meta/Tal et al.,\(^50\) reviewed patterns of practice in 124 bilateral prophylactic mastectomies performed within Ontario, Canada, during the years 1991–1999. Since 1995, when genetic testing for BRCA became available, the frequency of total mastectomy (compared to subcutaneous mastectomy) increased among women with a positive family history from 81.3% to 94.0% \((p = 0.07)\). Most (80.5%) of the patients underwent prophylactic mastectomy because of their family history or BRCA1 or BRCA2 status. About 80% of the patients were younger than 50 years old at the time of surgery (mean age 43.5 years). Similarly, in the descriptive study by Scheuer et al.,\(^30\) the 29 women (of 194 carriers of BRCA1 mutations), who chose to undergo prophylactic mastectomy after receiving the genetic tests results, were significantly younger than women who declined surgery (mean age 43.0 vs. 46.8, respectively; \(p = 0.015\)).

Since bilateral prophylactic mastectomy seems a rather drastic procedure, its psychological and sexual impact was assessed in a study by Hatcher et al.,\(^51\) Women who had accepted surgery \((n=79)\) were more likely than women who had declined surgery \((n=64)\) to believe it inevitable that they would develop breast cancer (32% vs. 10%; \(p = 0.003\)). Among the women who have undergone prophylactic mastectomy, the frequency of those who were scored as having a possible psychological morbidity decreased significantly over time by 17% (95% CI: 2–32%) and 31% (95% CI: 15–47%) at 6 and 18 months postoperatively. Smaller and nonsignificant decreases were found among the women who declined surgery (14% and 16% at 6 and 18 months since they declined surgery). The level of sexual discomfort and degree of sexual pleasure did not change significantly over time in either of the 2 groups.

Two decision analyses assessed the life expectancy gains by preventive strategies for breast and ovarian cancer among BRCA1\(^52\) or BRCA1 or BRCA2\(^53\) mutation carriers. According to both models, the life expectancy gains were highest if both prophylactic oophorectomy and bilateral mastectomy were performed; however, the authors suggest that taking into account women’s preferences, prophylactic oophorectomy tends to be
better strategy for women at high risk, when performed before the age of 40. According to the analysis by Grann et al.,\textsuperscript{53} the maximal quality adjusted survival results from prevention with both prophylactic oophorectomy and tamoxifen.

Nevertheless, these decision analyses are based upon data that are partial at best and often theoretical.

The acceptability of different preventive measures was studied among 355 French, Canadian and English women at high risk for breast cancer according to family history who were unaware of their genetic status.\textsuperscript{54} Surveillance with routine mammography was the most acceptable procedure. The acceptance of the test increased with age of performance; thus, 31% accepted performance of mammography starting at age 25 years compared to 87% at age 50. Chemo prevention by tamoxifen was accepted by 60% of women, and 60% found oophorectomy after the age of 50 years acceptable. Prophylactic mastectomy was the least accepted alternative — only 16% agreed to undergo the operation before the age of 35, and 29% accepted the operation after the age of 50. Acceptance rates for tamoxifen and oophorectomy were significantly higher among British women. The rates were significantly lower for mastectomy among the French women. Agreement with the procedures was correlated with the belief that breast cancer ran in the family.

In conclusion, although prophylactic mastectomy currently seems to promise the most effective prevention, it is the least acceptable procedure among women, and there is little information on the effectiveness of the other measures in preventing breast cancer and improving survival. Therefore, the current body of knowledge does not allow a woman or her physician to confidently make long-term decisions.

REFERENCES


52. van-Roosmalen MS, Verhoef LCG, Stalmeier PFM, Hoogerbrugge N, van den Ouweland AM, Niermeijer MF, Brekelmans CT, Klijn JG. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2001;345:159–64.