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Preventive mastectomy in patients at breast cancer risk due to genetic alterations in the *BRCA1* and *BRCA2* gene

Received: 4 November 2002
Accepted: 17 January 2003
Published online: 21 February 2003
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Abstract *Background:* The availability of genetic testing for inherited mutations in the *BRCA1* and *BRCA2* gene provides potentially valuable information to women at high risk of breast and ovarian cancer. *Methods and focus:* We review the literature on the value of prophylactic surgical strategies in patients with hereditary predisposition to develop breast cancer and discuss the surgical options available in high-risk cancer patients, decision analyses, and possible complications. *Results:* Preventive surgical interventions to reduce

cancer risk in high-risk patients are often strongly recommended. A patient's life-time risk to develop breast cancer in the presence of *BRCA1* and *BRCA2* mutations is 50–90%. Despite the reduction in the risk of developing breast cancer, prophylactic mastectomy often leads to significant physical and psychological sequelae.

Keywords *BRCA1* · *BRCA2* · Prophylactic mastectomy · Breast cancer · Oophorectomy

Introduction

The *BRCA1* and *BRCA2* genes encode proteins that participate in the cellular response to DNA damage; inactivating mutations in these genes increase susceptibility to breast and ovarian cancer. *BRCA1* and *BRCA2* mutations were first identified in 1994 [1, 2]. Tests for *BRCA1* and *BRCA2* mutations are now widely available and are performed increasingly on samples taken from women who were diagnosed with breast or ovarian cancer at a young age, or whose first-degree relatives have experienced a cancer of this kind (families with three affected members in a maternal or paternal lineage over the course of three generations).

The prevalence of germline (inherited) *BRCA1* and *BRCA2* mutations in the general population is 0.1–0.2%. Overall these mutations contribute only to a small fraction of all cases of breast cancer, but as many as 10% of cases diagnosed in women younger than 40 years of age and approximately 75% of familial cases occur in carriers of these mutations.

Women who carry germline *BRCA1* and *BRCA2* mutations have a strongly increased risk of breast and ovarian cancer. The cumulative risk is estimated to range from 40% to 85% for breast cancer and from 5% to 60% for ovarian cancer, depending on the population from which the data were derived [3]. With the known and theoretical limitations of breast and ovarian cancer surveillance and chemoprevention strategies in *BRCA1* and *BRCA2* mutation carriers it is understandable that many of these women and their clinicians have an interest in prophylactic surgery as a cancer risk reduction strategy.

Even if precise estimates of the efficacy of prophylactic surgery were available, decisions concerning whether or when to undergo these procedures would be complex and ultimately individual. The magnitude of the potential benefit depends on the risk of cancer associated with specific mutations, the prognosis of the tumors in carriers of mutations, and the extent to which relief of anxiety could result from surgical prophylaxis. These benefits must be weighed against an array of potential surgical complications and the impact of mastectomy or oopho-

rectomy on a woman's self-image and potential social consequences of such a decision.

To address this clinical dilemma we discuss the current literature on surgical options in *BRCA1* and *BRCA2* mutation carriers.

Prophylactic mastectomy: surgical considerations

Two different techniques are currently performed, and the choice between the two requires detailed discussions with the woman herself. The first is subcutaneous mastectomy (SCM) which preserves the nipple areola complex, with a certain amount of breast tissue remaining behind the nipple and the areola. This procedure is less mutilating, but it does not completely avoid the risk of cancer developing in the remaining breast tissue. The second option is skin-sparing mastectomy with complete removal of the nipple areola complex.

Surgical complications

Any surgical procedure is associated with potentially adverse outcomes that should be considered when recommending an elective prophylactic procedure to a healthy woman. There is little information about the complications of mastectomy performed for the prevention of breast cancer. The rate of surgical complications in a series of 163 patients who had SCM between 1974 and 1980 has been reported [4]. More than 80% of the procedures were bilateral prophylactic mastectomies. The reported incidence of hematoma was 14%, the incidence of pain was 9%, and that of nipple necrosis and infection was 6%. However, these data were obtained with surgical techniques in use 20 years ago and most likely do not reflect current standards of practice.

Reconstructive surgery

Reconstructive surgery can be performed either with prosthetic material or by autologous tissue transfer. There is still some debate as to whether this procedure should be immediate or delayed in breast cancer patients. In general the concerns regarding immediate reconstruction are related to potential adverse effects on the subsequent ability to administer radiation or chemotherapy and do not apply to the prophylactic setting.

Breast reconstruction with autologous material

The best cosmetic results are usually obtained with autologous tissue reconstruction either by the free or pedicled transverse rectus abdominal musculocutaneous flap

or by musculocutaneous latissimus dorsi flap. The shape of the breast can be reconstructed very well with a musculocutaneous flap; the volume required varies depending on the original volume of the breast. The main drawback associated with the musculocutaneous flap technique is an additional abdominal or dorsal scar and the risk of abdominal or dorsal sequelae.

Breast reconstruction with prosthetic material

After mastectomy the retromuscular plan is undermined and wide enough to allow good symmetry once the prosthesis has been introduced. The controversy over the medical complications of silicone implants is widely reflected in the literature. It is preferable to use saline implants which can be filled in situ to introduce the prosthesis more easily and to prevent damage to scar margins. Modifications in shape and consistency occur in 15–20% of cases and can become evident as late as several months or years after breast reconstruction [5]. The most common indications for surgical interventions after implant reconstruction of the breast are capsular contraction, implant rupture, hematoma, and wound infection. A study of 92 women who had implant reconstruction after prophylactic mastectomy reported that the 5-year cumulative incidence of complications requiring surgical intervention was as high as 30.4% [6].

Efficacy of prophylactic mastectomy

Most data on the efficacy of prophylactic mastectomy are based on retrospective analysis of patients at high risk. Only one study has evaluated this question prospectively, although patients were not randomized (Table 1). Women at high risk are often not ready to participate in a prospective randomized trial in prophylactic breast surgery. Tambor et al. [7] assessed patients' willingness to participate in hypothetical research studies for breast and ovarian cancer risk reduction. After counseling sessions for *BRCA1* and *BRCA2* in 87 at-risk women, only 19% for breast cancer and 17% for ovarian cancer were willing to participate in such a trial. It seems unlikely that a large cohort of high-risk women could be motivated to participate in a trial in which they would be randomized to have their breasts surgically removed or not. Greater feasibility combined with fewer ethical concerns make nonrandomized trials a more viable alternative to randomized trials in terms of evaluating preventive interventions for breast and ovarian cancer when prophylactic surgery is one of the investigated treatments.

Meijers-Heijboer et al. [8] conducted a prospective study of 139 women with a pathogenic *BRCA1* or *BRCA2* mutation who were enrolled in a breast-cancer surveillance program at the Rotterdam Family Cancer

Table 1 Published series of patients with bilateral prophylactic breast surgery

	Meijers-Heijboer et al. [8]	Hartmann et al. [9]	Penissi and Capozzi [10]
<i>n</i>	139	639	1500
Analysis	Prospective	Retrospective	Retrospective
Median follow-up (years)	3	14	9
Surgical strategy	Total mastectomy	90% SCM, 10% total mastectomy	SCM
Expected breast cancer incidence	8/63	Moderate risk 37.4/425, high risk 30/214	Not stated
Observed breast cancer incidence	0/76	Moderate risk 4/425, high risk 3/214	6/1046
Risk reduction (95%CI)	Hazard ratio 0 (0–0.36), $P=0.003$	90% (70.8–97.9)	Not stated

Clinic. At the time of enrollment none of the women had a history of breast cancer. Of these women 76 eventually underwent prophylactic mastectomy, and the other 63 remained under regular surveillance. The effect of mastectomy on the incidence of breast cancer was analyzed by the Cox proportional hazards method in which mastectomy was modeled as a time-dependent covariate. No cases of breast cancer were observed after prophylactic mastectomy after a mean follow-up of 2.9 ± 1.4 years, whereas eight breast cancers developed in women under regular surveillance after a mean follow-up of 3.0 ± 1.5 years [hazard ratio 0, 95% confidence interval (CI) 0–0.36, $P=0.003$]. The actuarial mean 5-year incidence of breast cancer among all women in the surveillance group was $17\pm 7\%$. On the basis of an exponential model the annual incidence of breast cancer in this group was 2.5%. The observed number of breast cancers in the surveillance group was consistent with the expected number (ratio of observed to expected cases 1.2, 95% CI 0.4–3.7, $P=0.80$). In women with a *BRCA1* or *BRCA2* mutation undergoing prophylactic bilateral total mastectomy reduces the incidence of breast cancer at 3 years of follow-up.

A retrospective cohort analysis of efficacy was carried out in 639 women with a family history of breast cancer who had bilateral SCM (90%) or total mastectomy (10%) and were treated at the Mayo Clinic between 1960 and 1993 [9]. Approximately two-thirds of the women were classified as being at high risk on the basis of some features of autosomal dominant breast-ovarian cancer syndrome (multiple cases of breast and/or ovarian cancer in close relatives, including early onset and bilateral disease). A subgroup at moderate risk was also defined to include all other women with a family history of breast cancer who failed to meet the more stringent high-risk criteria. A control study involving high-risk probands' sisters was included together with the Gail model to estimate the efficacy of surgery and to calculate the number of breast cancers expected in these two groups in the absence of prophylactic mastectomy.

Of 639 women with a family history of breast cancer who had undergone bilateral prophylactic mastectomy 214 were identified to be at high risk and 425 at moder-

ate risk. The median length of follow-up was 14 years. The median age at prophylactic mastectomy was 42 years. By the Gail model 37.4 breast cancers were expected in the moderate-risk group; 4 breast cancers occurred (reduction in risk 89.5%, $P<0.001$). The number of breast cancers among the 214 high-risk probands was compared to that among their 403 sisters who had not undergone prophylactic mastectomy. Of the latter 156 (38.7%) had been given a diagnosis of breast cancer (115 cases were diagnosed before the respective proband's prophylactic mastectomy, 38 were diagnosed thereafter, and the time of diagnosis was unknown in 3). By contrast, breast cancer was diagnosed in 3 of 214 (1.4%) of the probands. Thus, prophylactic mastectomy was associated with a reduction in the incidence of breast cancer of at least 90%.

Pennisi and Capozzi [10] reported another retrospective analysis of 1500 patients who underwent SCM. These authors' data suggest that most patients treated with SCM experienced proliferative fibrocystic or macrocystic disease, among other high-risk factors. The data also suggest that thoroughly performed SCM is an effective means of providing prophylaxis in women who are at high risk for breast cancer. In 39% of the study subjects there was a family history of breast cancer in at least one first- or second-degree relative. The mean follow-up time was 9 years; 88% of the patients were younger than 50 years of age at time of surgery. The 10-year incidence of breast cancer after prophylactic mastectomy was 0.57% (six cases), but 30% of the patients were lost to follow-up, giving a slight underestimation of the true incidence of breast cancer after prophylactic mastectomy [11].

Other prophylactic surgical options: prophylactic oophorectomy

Preventive surgery of the breast in *BRCA1* and *BRCA2* carriers is not limited to removal of breast tissue. Prophylactic oophorectomy is another surgical option that has received attention as risk-reducing management procedure in high-risk patients. Recently reported data sup-

Table 2 Studies of prophylactic oophorectomy

	Rebeck et al. [12]	Kauff et al. [13]
<i>n</i>	551	170
Analysis	Retrospective	Prospective
Follow-up (years)	9 (ovarian) 11 (breast)	2
Ovarian cancer incidence		
Surveillance group	58/292 (19.9%)	5/72 (6.9%)
Oophorectomy group	8/259 (3.1%)	4/98 (4.1%)
Breast cancer incidence		
Surveillance group	60/142 (42.3%)	8/62 (12.9%)
Oophorectomy group	21/99 (21.2%)	3/69 (4.3%)

port the beneficial effect of salpingo-oophorectomy in these patients after the completion of childbearing.

Decreases in ovarian hormone following bilateral oophorectomy appear to reduce the cancer risk among *BRCA1* mutation carriers (Table 2). Rebeck et al. [12] report the results of a multicenter, retrospective analysis of 551 women carrying mutations in either *BRCA1* or *BRCA2*. Ovarian cancer developed in 58 of 292 women (19.9%) who underwent surveillance during a mean follow-up of 9 years. By contrast, stage I ovarian cancer was identified in only 6 of 259 women (2.3%) who underwent bilateral prophylactic oophorectomy; primary peritoneal cancer subsequently developed in another 2 (0.8%). During 11 years of follow-up breast cancer was diagnosed in 60 of the 142 women (42.3%) with no history of breast cancer who were followed conservatively, compared with 21 of the 99 similar women (21.2%) who had undergone prophylactic oophorectomy.

Kauff et al. [13] reported the results of a prospective study of 170 *BRCA* mutation carriers with a mean follow-up of 2 years. Ovarian cancer or a papillary serous carcinoma of the peritoneum developed in five of 72 women who elected intensive surveillance (6.9%). Among 98 women who underwent prophylactic salpingo-oophorectomy three had early-stage tumors that were diagnosed at the time of surgery (3.1%), and primary peritoneal cancer developed in one patient during follow-up (1%). Among women who had not undergone prophylactic bilateral mastectomy breast cancer developed in 8 of 62 in the surveillance group (12.9%), and in 3 of 69 in the oophorectomy group (4.3%).

Decision analysis

The likelihood of an individual patient considering risk-reduction surgery is not necessarily correlated with actually calculated risk. Meiser et al. [14] questioned 333 women who were awaiting their initial appointments for risk assessment, advice regarding surveillance, and pro-

Table 3 Decision analysis in a hypothetical cohort of women carrying mutations of *BRCA1* and *BRCA2*; estimated gains in life expectancy in a 30-year-old woman

	Schrag et al. [15]	Grann et al. [16]
Statistical model	Markov model	Markov model
Years gain in life expectancy		
Mastectomy	2.9–5.3	3.5
Oophorectomy	0.3–1.7	2.6
Estimated risk reduction in breast cancer associated with		
Mastectomy	85%	90%
Oophorectomy	40%	Not stated

phylactic options at one of 14 familial cancer clinics participating in a cross-sectional, questionnaire-based survey. The women were asked whether they would consider prophylactic mastectomy if genetic testing identified a mutation in a breast cancer-predisposing gene; 19% said yes, 47% said no, 34% were unsure, and 1% had already undergone prophylactic mastectomy. Bivariate analysis showed the highest proportion of women, 25%, reporting that they would consider prophylactic mastectomy among those at moderately increased risk of developing breast cancer, while only 16% of those at high risk did so. Multivariate analyses revealed that consideration of prophylactic mastectomy was strongly correlated with high levels of breast cancer anxiety [odds ratio (OR) 17.4, 95% CI 4.35–69.71, $P=0.0001$] and overestimation of one's breast cancer risk (OR 3.01, 95% CI 1.43–6.32, $P=0.0036$) while there was no association with objective breast cancer risk ($P=0.60$).

Means are available for the hypothetical calculation of gains in life expectancy in a 30-year-old woman carrying a mutation of *BRCA1* and *BRCA2* related to prophylactic surgical procedures (Table 3). Schrag et al. [15] reported a decision analysis comparing prophylactic mastectomy and prophylactic oophorectomy with no prophylactic surgery among *BRCA1* and *BRCA2* carriers. On average 30-year-old women who carry *BRCA1* or *BRCA2* mutations gain 2.9–5.3 years of life expectancy from prophylactic mastectomy and from 0.3–1.7 years of life expectancy from prophylactic oophorectomy, depending on their cumulative risk of cancer. Gains in life expectancy decline with age at the time of prophylactic surgery and are minimal for 60-year-old women. Among 30-year-old women oophorectomy may be delayed by 10 years with little loss of life expectancy.

Similar findings have been published by Grann et al. [16]. Markov modeling of outcomes was performed in a simulated cohort of 30-year-old women who tested positive for *BRCA1* and/or *BRCA2* mutations. The model incorporated breast and ovarian cancer incidence rates from the literature and mortality rates from the Surveil-

lance, Epidemiology, and End Results Program. A 30-year-old woman was able to prolong her survival beyond that associated with surveillance alone by use of preventive measures: 1.8 years with tamoxifen, 2.6 years with prophylactic oophorectomy, 4.6 years with both tamoxifen and prophylactic oophorectomy, 3.5 years with prophylactic mastectomy, and 4.9 years with both surgeries. Quality-adjusted survival was improved by 2.8 years with tamoxifen, by 4.4 years with prophylactic oophorectomy, by 6.3 years with tamoxifen and oophorectomy, and by 2.6 years with mastectomy or with both surgical modalities. The benefits arising from all of these strategies would decrease if they were initiated at later ages.

Concerns about prophylactic surgery

We know very little regarding the psychosocial sequelae experienced by women following bilateral prophylactic mastectomy. Women's regret following preventive breast surgery is a major consideration that must be addressed preoperatively with these patients. In a study performed among 370 women having undergone prophylactic mastectomy at the Memorial Sloan-Kettering Cancer Center 21 expressed regret about their decision [17]. The most common regrets were articulated in physician-initiated rather than patient-initiated discussions about the preventive breast surgery procedure. Psychological distress and the lack of psychological and rehabilitative support throughout the process were reported, and there were additional regrets about prophylactic mastectomy cosmesis, perceived difficulty of detecting breast cancer in the remaining breast tissue, surgical complications, residual

pain, lack of education about the procedure, concerns about consequent body image, and sexual dysfunction.

The Manchester protocol [18] assessed mental health and body image outcomes in 52 patients after bilateral prophylactic mastectomy using self-report questionnaires, the General Health Questionnaire and the Body Image Scale. No negative change in body image was reported by 21% of women following surgery and the majority of changes that were reported were of only a minor degree. The most frequently reported changes were in sexual attractiveness (55%), feeling less physically attractive (53%), and self-consciousness about appearance (53%); one-third of women felt less feminine to a minimal degree. A minority of women had more serious psychological or body image concerns, usually in relation to surgical complications.

Conclusions

Prophylactic surgery reduces the likelihood of developing breast cancer among women at heightened risk for breast cancer, but at significant personal risk. Thus *BRCA1* and *BRCA2* testing must be performed to obtain objective confirmation of the genetic risk. Although prophylactic mastectomy statistically reduces the chances of a woman at high risk of developing breast cancer, the possibility of significant physical and psychological sequelae remains. Counseling these woman preoperatively is highly recommended since the ultimate decision must be made after individual risk assessment and thorough weighing of advantages and disadvantages associated with such a strategy.

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