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PROPHYLACTIC MASTECTOMY

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Prophylactic mastectomy reduces the likelihood of developing breast cancer among women at heightened risk for breast cancer, but at significant personal cost. Women at increased breast cancer risk on the basis of hormonal history, family history and/or genetic mutation carrier status may consider bilateral prophylactic mastectomy with or without reconstruction to reduce their cancer risk and/or decrease their chances of cancer mortality. Women having received mastectomy as treatment for breast cancer may request contralateral mastectomy to decrease the chances of developing a second breast primary. The potential oncologic value of these procedures must be weighed carefully on a case-by-case basis against the operation's physical and psychological morbidity.

Prophylactic surgery for breast cancer remains an option for high-risk patients, because the alternatives are also highly imperfect.

High-risk patients, such as carriers of BRCA-1 or BRCA-2 mutations, tend to develop breast cancers at young ages. Intensive surveillance may fail to detect breast carcinoma at an early, curable stage, particularly in younger women. Tumors grow at highly variable rates, but on average have higher proliferation rates when women are premenopausal. This difficulty in increased, because premenopausal women tend to have breast tissue of higher density that tends to compromise cancer detection by mammography. All women may improve their overall health and thus perhaps minimize breast cancer risk by maintaining a healthy weight, avoiding cigarettes, limiting alcohol consumption, getting regular exercise, and avoiding non-diagnostic ionizing radiation. Nevertheless, no lifestyle modifications have yet been proven to prevent or definitively lower the risk of breast cancer (1). Chemoprevention is early in its development and uses drugs with significant side-effects and complications. While advances in chemoprevention, screening technology, or breast carcinoma treatment exist, for the time being prophylactic mastectomy has attributes that make it an alternative that must be considered (2).

The alternative to breast cancer treatment is breast cancer prevention. Cancer develops because malignant transformation occurs in the cells within the ductal and lobular epithelium. To prevent the development of cancer, we can directly alter the cells so they are less likely to undergo malignant transformation (gene therapy), or change the biological environment such that these cells are less likely to transform (chemoprevention), or we can eradicate the cells by removing them from the host (surgical risk reduction). In discussing the relative benefits and risks associated with surgical risk reduction, major questions regarding breast cancer risk reduction include the following:

1. What are the risks and benefits of risk reduction breast surgery?
2. What operations are currently available for surgical risk reduction?
3. How should patients be selected for risk reduction surgery?

Risks and benefits of breast cancer surgical risk reduction

Cancer risk among women with genetic predisposition for breast cancer. Five to ten per cent of breast cancer results from an inherited germ line mutation. The main susceptibility genes are BRCA1 and BRCA2, but others include Cowden's disease, Li Fraumeni syndrome and ataxia-telangiectasia. For those with BRCA1 or BRCA2 mutations the lifetime probability of breast cancer is between 0.40 and 0.73. The efficacy of surveillance in women with genetic susceptibility has yet to be proved. Prophylactic bilateral mastectomy will probably reduce the risk of breast cancer but this may not be absolute because of the difficulty of removing all breast tissue (3). Genetic testing needs to be offered to young women with breast cancer before considering testing their relatives. Based on expert opinion concerning presumptive benefit, early breast cancer and ovarian cancer screening are recommended for individuals with BRCA1 mutations and early breast cancer screening for those with BRCA2 mutations. Prophylactic surgery (e.g., mastectomy, oophorectomy) is an option for mutation carriers, but case reports have documented the occurrence of cancer following prophylactic surgery (4).

Unfortunately, bilateral mastectomy does not guarantee that a woman will not get breast cancer. Breast cancer has been reported after prophylactic subcutaneous mastectomy for breast cancer (5, 6). These occurrences can develop as late as 40 years following surgery (7). For this reason, decision-making for or against prophylactic surgery requires weighing the risks and benefits, which can be done in a quantitative fashion for populations of women at risk.

Contralateral cancer risk in patients with unilateral cancers. Women previously treated for primary operable breast cancer are at increased risk of developing cancer in the contralateral breast. Kollias and colleagues performed a retrospective study of 3211 women aged 70 years and younger treated for primary operable breast cancer between 1975 and 1995. Among these, 83 developed CBC prior to locoregional or distant recurrence from the first primary. The clinical incidence of CBC was 6.4 per 1000 women years, three to four times the risk of occurrence of breast cancer in the general female population (or a risk of six to eight times

to the remaining breast). Strong family history, age of onset<50 years and lobular histology were significant factors predicting for CBC in univariate and multivariate models. Other clinical factors (previous hormone therapy, chemotherapy, radiotherapy) or histological factors (DCIS, invasive tumor size, grade, vascular invasion, lymph node and estrogen receptor status) were not significant predictors for CBC. The authors concluded that in women previously treated for primary operable breast cancer, early age of onset and a strong family history are predictors for the subsequent development of metachronous CBC. Ipsilateral mastectomy with contralateral prophylactic mastectomy with or without immediate breast reconstruction is a reasonable option for a young woman diagnosed with breast cancer and who has a strong family history, particularly if the cancer has histological features suggesting a good prognosis (8).

If one is contemplating a contralateral prophylactic mastectomy in a breast cancer patient with a known BRCA1/2 mutation, the age at diagnosis of the first cancer should be considered in making this decision. Verhoog and colleagues studied the contralateral breast cancer risk in 164 patients from 83 families with a proven BRCA1 mutation in relation to the age at diagnosis of the first primary breast cancer. In the actuarial outcomes after 10 years' follow-up, 40% of the 124 BRCA1-patients diagnosed with breast cancer <50 years had developed contralateral breast cancer, Vs 12% of the 40 patients >50 years at first diagnosis (P = 0.02) (9).

Invasive lobular carcinoma (ILC) and contralateral breast cancer risk. The incidence of contralateral breast cancer is heightened with ILC, creating controversy about the management of the contralateral normal-appearing breast. Lee and colleagues reviewed the case histories of 419 patients with histologically proven ILC who underwent definitive surgery at their institution from 1978 to 1991. Of the 419 women with ILC, 36 (8.6%) had bilateral cancer, with a cumulative risk of 10% at 10 years. Twenty-five (69%) of these cancers were suspected before operation. From 105 contralateral prophylactic surgical procedures, seven (64%) in-situ and four (36%) invasive cancers were detected. The age at presentation and multifocality of the index cancer were significantly different between patients with unilateral and those with bilateral cancers. No survival difference was noted between patients whose contralateral cancers were suspected clinically and those whose cancers were detected prophylactically. Survival rates between patients with unilateral versus bilateral cancers were also not different. However, patients with contralateral prophylactic surgery had a better prognosis than those with unilateral tumors and no prophylaxis. The authors concluded that 10% of patients with ILC experienced bilateral cancers during a period of 10 years. Survival was not influenced by the development of a second cancer, but it improved with surgical prophylaxis (10).

Not all studies show risk of contralateral breast cancer to be markedly different between invasive ductal and lobular histologies. Yeatman and colleagues performed a study to evaluate the tumor biology with respect to bilaterality and recurrence rates for bilateral ILC in comparison with other histological types. Among 116 patients with documented bilateral breast cancer (invasive or in situ), 82 patients (70.7%) had metachronous breast cancer, and 34 (29.3%) had synchronous cancer. Although median follow-up times were short, the risk of developing breast cancer in the contralateral breast after the diagnosis of cancer in the ipsilateral breast was estimated to be 0.7% per patient-year of follow-up. ILC cancers recurred 8.1% of the time, whereas invasive ductal cancers recurred at a rate of 7.8%. Recurrences were equally divided between local and distant sites. Thus, although ILC cancers have demonstrated insidious behavior, their incidence of bilaterality appeared to be only slightly higher than other histologies. Furthermore, their rates of recurrence appeared to be low when properly evaluated and treated. The authors concluded that their data do not support the routine use of blind contralateral biopsy or prophylactic mastectomy among the general population of breast cancer patients (11).

Clinical data regarding surgical prophylaxis. The best clinical data regarding the relative value of prophylactic mastectomy suggests that the operation reduces the risk of developing breast cancer by approximately 90%, both among moderate risk and high risk patients. Hartmann and colleagues conducted a retrospective study of all women with a family history of breast cancer that underwent bilateral prophylactic mastectomy at the Mayo Clinic between 1960 and 1993. The women were divided into two groups - high risk and moderate risk - on the basis of family history. A control study of the sisters of the high-risk probands and the Gail model were used to predict the number of breast cancers expected in these two groups in the absence of prophylactic mastectomy. The authors identified 639 women with a family history of breast cancer who had undergone bilateral prophylactic mastectomy: 214 at high risk and 425 at moderate risk. According to the Gail model, 37.4 breast cancers were expected in the moderate-risk group; 4 breast cancers occurred (reduction in risk, 89.5 percent; P<0.001). They compared the numbers of breast cancers among the 214 high-risk probands with the numbers among their 403 sisters who had not undergone prophylactic mastectomy. Of these sisters, 38.7 percent (156) had been given a diagnosis of breast cancer (115 cases were diagnosed before the respective proband's prophylactic mastectomy, 38 were diagnosed afterward, and the time of the diagnosis was unknown in 3 cases). By contrast, breast cancer was diagnosed in 1.4 percent (3 of 214) of the probands. Thus, prophylactic mastectomy was associated with a reduction in the incidence of breast cancer of at least 90 percent. The authors concluded that women with a high risk of breast cancer on the basis of family history, prophylactic mastectomy may significantly reduce the incidence of breast cancer (12).

A European prospective, nonrandomized study by Meijers-Heijboer and colleagues suggests that women with BRCA1 and BRCA2 mutations have short-term benefit from prophylactic bilateral mastectomy (13). The investigators directed a breast-cancer surveillance program at the Rotterdam Family Cancer Clinic. In their registry, 139 women with a pathogenic BRCA1 or BRCA2 mutation

were enrolled. None of these women had a history of breast cancer. Seventy-six of these women eventually underwent prophylactic mastectomy, and the other 63 remained under regular surveillance. No cases of breast cancer were observed after prophylactic mastectomy after a mean follow-up of 2.9 years, whereas eight breast cancers developed in women under regular surveillance after a mean follow-up of 3.0 years (P=0.003). The actuarial mean five-year incidence of breast cancer among all women in the surveillance group was 17 percent. On the basis of an exponential model, the yearly incidence of breast cancer in this group was 2.5 percent. The authors concluded that in women with a BRCA1 or BRCA2 mutation, prophylactic bilateral total mastectomy reduces the incidence of breast cancer at three years of follow-up.

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