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Contralateral risk-reducing mastectomy in young women

Belén Merck¹

Fundación Instituto Valenciano de Oncología, Valencia, Spain.

Corresponding author:

Belén Merck, MD

Department of Surgery

Fundación Instituto Valenciano de Oncología

Calle Profesor Beltrán Báuena, 8

46009-Valencia. Spain

E-mail: belenmerck@yahoo.es

Phone: +34 96 111 40 19

Fax: +34 96 111 40 18

Introduction

Contralateral risk-reducing mastectomy consists in the surgical removal of the contralateral breast to reduce the risk of breast cancer there [1].

Patients with unilateral primary breast cancer have an increased risk of developing a contralateral breast cancer [2]. In a large-scale study, Quan et al [3] evaluated the incidence, stage and outcomes of women with contralateral synchronous (defined as tumors diagnosed within 12 months of the initial diagnosis) and metachronous (tumors diagnosed beyond 12 months after the initial diagnosis) breast cancer over a 9-year study period. In the 28787 cases of breast cancer identified, the mean annual incidence of contralateral breast cancer was 0.1%, while the cumulative incidence of contralateral synchronous cancer was 2.1%, and the cumulative incidence of metachronous cancer was 1.2%.

Using the Surveillance, Epidemiology and End Results database (SEER), Gao et al [4] found that the 5-, 10-, 15-, and 20-year actuarial incidence of developing contralateral breast cancer was 3%, 6%, 9% and 12%, respectively. The average incidence of contralateral breast cancer per year of follow-up per patient was estimated at 0.6%. Based on these, and other retrospective studies, the incidence rate of contralateral breast cancer in breast cancer patients has been estimated to range from approximately 0.5% to 1.8% per year.

Benefits of contralateral risk-reducing mastectomy

Existing data suggest that contralateral risk-reducing mastectomy may diminish by as much as 95% the risk of developing breast cancer in moderate- and high-risk women, particularly in women with ipsilateral breast cancer or known BRCA1/BRCA2 mutation [2, 5, 6]. Using the Anderson model to predict the risk of developing contralateral breast cancer, McDonnell et al [7] estimated that contralateral risk-reducing mastectomy resulted in a risk reduction of 64%.

However, contralateral risk-reducing mastectomy does not completely eliminate the risk of contralateral cancer, and to date, due to lack of prospective and randomized trials, there is no evidence to support that it improves overall survival [8, 9].

Despite these inconclusive data, with increasing frequency women are undergoing risk-reducing mastectomy. Using the SEER database, Tuttle et al [10] reviewed the treatment trends of patients with unilateral breast cancer diagnosed from 1998 through 2003, and found that the overall rate of contralateral risk-reducing mastectomy more than doubled during the 6-year period, increasing from 2% in 1998 to 5% in 2003 in all cancer stages. In their study, being non-Hispanic white, having a tumor with lobular histology, a previous diagnosis of cancer and/or younger age were associated with significantly higher rates of contralateral risk-reducing mastectomy. Logistic regression analysis demonstrated that young age was associated with higher rates of contralateral risk-reducing mastectomy (7% of all surgically treated patients < 39 years old underwent contralateral risk-reducing mastectomy compared with only 1.3% of women \geq 70 years old) [10].

Additional factors influencing the rate of contralateral risk-reducing mastectomy identified in other population-based studies are a large tumor size (> 5 cm vs. 2 cm), the presence of multicentric disease, a positive lymph node status, being treated by a female surgeon [11], physician advice regarding the risk of contralateral breast cancer, patient's fear of developing another tumor, desire for cosmetic symmetry, family history of breast cancer, difficulty in screening for breast cancer, or a combination of all these reasons [12, 13].

Risk factors for contralateral breast cancer

Recently, Yi et al [12] performed a matched case-control study to identify the clinical and pathologic factors of primary breast cancer that would predict a breast cancer, as well as moderate to high-risk histological features in the contralateral breast. They

found that patient's age at diagnosis, a 5-year Gail risk \geq 1.67%, an invasive lobular histology, an additional ipsilateral moderate to high-risk pathological findings or an ipsilateral multicentric tumor were significant predictors of contralateral breast cancer. Of these, an invasive lobular histology or multicentric tumor and a 5-year Gail risk \geq 1.67% were identified as independent predictors of malignancy in the opposite breast. Conversely, estrogen and progesterone receptor status, previous hormone replacement therapy and first-degree family history of breast cancer were not associated with an increased risk of contralateral breast cancer. Multivariate analysis also revealed that an age \geq 50 years at the time of the initial cancer diagnosis and an additional ipsilateral moderate to high-risk lesions were independent predictors of moderate- to high-risk histologic findings in the contralateral breast [12].

The *BRCA* gene mutation status should always be considered when evaluating a patient's risk of contralateral breast cancer, particularly in young women. *BRCA1/2* mutation carriers have a significantly higher risk of developing contralateral breast cancer, with an estimated 10-year risk ranging from 20-42% compared with a 5-6% risk in no-carriers. These patients usually tend to be much younger at diagnosis than sporadic cases of breast cancer [14].

In a prospective trial involving 491 women with stage I or II breast cancer and a *BRCA1* or *BRCA2* mutation, factors predictive of a reduced risk were the presence of a *BRCA2* mutation, age over 50 years at first diagnosis, use of tamoxifen and bilateral oophorectomy. This latter factor was particularly strong in women diagnosed before age 49. In women without bilateral oophorectomy or not receiving adjuvant tamoxifen, the risk of developing contralateral breast cancer was 43% for *BRCA1* and 35% for *BRCA2* mutation carriers at 10 years [15].

Recommendations of the Society of Surgical Oncology

According to the Society of Surgical Oncology [16], contralateral risk-reducing mastectomy is indicated in patients with a current or previous diagnosis of breast cancer, for: (i) risk reduction in patients at high risk of contralateral breast neoplasm (i.e. patients with known mutations of *BRCA1/2* or other strongly predisposing breast cancer susceptibility genes; patients with a family history of breast cancer in multiple first-degree relatives and/or multiple successive generations of family members with breast and/or ovarian cancer; and a high-risk histology); (ii) patients in whom subsequent surveillance of the contralateral breast would be difficult because of mammographically dense breasts or diffuse indeterminate calcifications in the contralateral breast; and (iii) improved symmetry in patients undergoing mastectomy with reconstruction for the index cancer.

Surgical techniques for contralateral risk-reducing mastectomy

The surgical techniques most frequently used for contralateral risk-reducing mastectomy include:

(i) Total mastectomy, which involves the resection of the entire breast gland including the overlying skin and the nipple-areola complex. The axillary lymph nodes and pectoral muscle are left intact (Figure 1). This technique is generally perceived as a more robust procedure for breast cancer surgical prophylaxis. However, due to cosmetic issues, it is being performed less often [17]. Breast reconstruction is optional and can be performed at the time of the mastectomy (immediate) or weeks to years afterwards (delayed breast reconstruction).

(ii) Skin-sparing mastectomy is a technical modification of total mastectomy (Figure 2). In this procedure, all the skin overlying the breast is preserved, and only the gland and the nipple-areola complex are excised. The main difference from total mastectomy is that it avoids skin excision, thereby achieving a more natural breast reconstruction, and a more favorable aesthetic outcome. The most widely used incisions for this technique

include periareolar with or without lateral and/or medial extensions, periareolar elliptical, and mastopexy-type incisions [18].

(iii) Subcutaneous mastectomy, which is always associated with immediate breast volume replacement. Complete resection of the breast tissue is done through an inframammary or periareolar incision that spares the overlying skin and nipple-areola complex (Figure 3) [17]. In this procedure, the skin and nipple-areola complex are preserved. Although this technique can achieve excellent aesthetic results, major concerns exist regarding its efficacy in controlling local disease [19].

The complication rate in all techniques is mostly related to the associated reconstructive procedure, and include wound infections, seroma formation, hematoma, delayed wound healing, partial or complete necrosis of the nipple-areola complex, and implant- or miocutaneous flap-related complications [20]. Unfortunately, there are no randomized, prospective studies comparing the different techniques of risk-reducing mastectomy.

Conclusions

Contralateral risk-reducing mastectomy significantly reduces the risk of developing contralateral breast cancer. However, the procedure is aggressive, irreversible, and probably unnecessary in patients who are not at high risk to develop contralateral disease. When facing a patient who wishes to undergo contralateral risk-reducing mastectomy, we have to be sure that the benefits outweigh complications. It is essential to identify the subgroup of patients whose contralateral breast cancer risk is high enough to benefit from surgery. Patients should be aware of the risk-reducing benefits of systemic adjuvant therapy, which reduces not only the risk of ipsilateral local failure, but also the incidence of contralateral breast neoplasm. According to the Society of Surgical Oncology, current indications for contralateral risk-reducing mastectomy include patients at high risk of contralateral breast cancer, patients in

whom subsequent surveillance of the contralateral breast would be difficult, and the requirement for improved symmetry. Recent publications indicate that young patients are especially prone to undergoing contralateral risk-reducing mastectomy. Therefore, selecting a surgical technique that yields favorable cosmetic results, yet at the same time fulfills its risk-reducing role, is imperative in these patients.

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Figure 1. Right breast: Status after radical modified mastectomy, adjuvant radiotherapy and differed *latissimus dorsi* flap reconstruction. Left breast: Prophylactic total mastectomy and immediate breast reconstruction with a tissue expander.



Figure 2. Skin-sparing mastectomy through a periareolar incision with lateral extension. Volume replacement, except for areolar reconstruction, with a de-epidermised *latissimus dorsi* flap, (Photograph kindly provided by J.L. Amaya and M. Correa).



Figure 3. Left breast: Total mastectomy and sentinel node biopsy and immediate reconstruction with a tissue expander. Second surgical procedure to replace tissue expander for a permanent implant. Areola tattooing. Right breast: Subcutaneous contralateral risk-reducing mastectomy and permanent implant placement.

