Risk-Reducing Mastectomy and Breast Reconstruction

Indications and Evidence for Current Management Strategies

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KEYWORDS

• Prophylactic • Risk reduction • Risk reducing • Mastectomy • Reconstruction • Surgery

KEY POINTS

- With increased exposure to genetic counseling and further understanding of the molecular specifics of breast cancer, risk-reduction surgery has become a hot topic for both patients and physicians.
- Risk-reduction surgery has been shown to decrease the incidence of breast cancer in women at elevated risk for developing breast cancer.
- Risk-reduction surgery has been shown to decrease the incidence of contralateral breast cancer, but data are limited on disease survival.
- There are data to recommend sampling lymph nodes in breasts without known abnormality in certain patients at high risk for occult abnormality.
- The indications for nipple areola–sparing mastectomy are changing as patients and physicians seek to achieve improved aesthetics in breast reconstruction while maintaining oncologically safe surgery.

INTRODUCTION

Each year there are an estimated 1.3 million new cancer cases and an estimated 550,000 deaths from cancer in United States. The lifetime probability of developing cancer in men is 43.5% and 38.34% for women. Breast cancer is the most common malignancy in women in North America and Western Europe. More than 225,000 cases of invasive breast cancer are diagnosed and more than 40,000 women will die from breast cancer each year. Breast cancer is second only to lung cancer as the cancer with highest moralities among that same group of women. About 15 million women in the United States seek medical attention each year with concern for or direct treatment of breast cancer.[1,2] Breast cancer diagnosis can be either sporadic or genetically predisposed, and multiple risk factors have been associated with increased risk for developing breast cancer. In contrast to genetic

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predispositions, there are also modifiable risk factors that can alter individual risk.[2]

As with all cancers, there is a constant effort toward early detection, early treatment, and prevention. With continued research in quantifying both genetic and modifiable risk factors, women are able to get a sense of their likelihood of developing breast cancer. For women already with a breast cancer diagnosis, certain risk factors and individual molecular abnormality may indicate the chance of developing breast cancer in the contralateral breast.

Bilateral risk-reduction mastectomy aims to decrease the incidence of breast cancer in women without a previous diagnosis, and contralateral risk-reduction mastectomy aims to prevent the incidence of contralateral breast cancer in a woman already diagnosed. Multiple factors have led to the increased prevalence of risk-reduction mastectomy procedures. The reason for more women choosing to pursue these surgical procedures can be attributed to the improved ease of genetic testing, increased public awareness, and advancement in reconstructive options and outcomes.

INDICATIONS FOR RISK-REDUCTION MASTECTOMY

Risk-reduction mastectomy is divided into 2 groups of surgical procedures. Bilateral risk-reduction mastectomy is the surgical removal of both breasts before any pathologic diagnosis has been made. In certain women with high risk for developing breast cancer in their life, it may be appropriate to surgically remove both breasts in hopes of preventing the incidence of breast cancer and decreasing breast cancer–specific mortality. Contralateral risk-reduction mastectomy is the surgical removal of a breast without any abnormality in a women diagnosed with unilateral breast cancer. The goal of contralateral mastectomy is to decrease the incidence of contralateral breast cancer. Although a goal, data have not shown an improvement in overall breast cancer mortality.

CONTROVERSIES FOR RISK-REDUCTION MASTECTOMY

The advancement of genetic screening, understanding of tumor molecular abnormality, and technical specifics of both the oncologic breast resection and reconstruction have contributed greatly to an increase in women seeking information about risk-reduction surgery. To inform patients appropriately, specific criteria guide patients and clinicians regarding for which patients the benefits outweigh the risks. As developments are made regarding risk factors, prevention, treatment, and reconstruction, the relative benefits of risk-reduction surgery may change.

Concurrent with risk-reduction mastectomy, the lymph node basin of unaffected breast can be assessed for occult abnormality. Assessing the lymph node drainage pathway of a breast for which no abnormality is detected may provide information regarding subsequent treatment were occult abnormality to be found. Although there is morbidity in assessing the lymph node basin, there may be cases in which the benefits outweigh the risks.

Advances in surgical breast oncology have coincided with advances in breast reconstruction. Nipple-sparing mastectomy is an important advancement in achieving a natural-appearing reconstructed breast, particularly when the incision is inconspicuously located in the inframammary fold. Preserving native breast skin and the native nipple areola complex allows for improved cosmetic breast reconstruction. In cases of risk-reduction surgery without a cancer diagnosis, it is generally accepted that nipple-sparing mastectomy achieves essentially equivalent risk reduction compared with skin-sparing mastectomy and simple mastectomy techniques.

EVIDENCE BASE FOR RISK-REDUCTION MASTECTOMY

A review of the literature was performed to explore the current indications for both bilateral and contralateral risk-reduction mastectomy. A selective literature review was performed by both authors using the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed). A PubMed search of English articles was completed with the search terms “breast cancer” AND “risk reduction mastectomy OR prophylactic mastectomy,” AND “indication,” and published between January 1st, 2007 and April 1st, 2017. An initial 26 papers resulted. One paper was excluded based on its status as an opinion piece.[3] No further paper was excluded. Each article was further analyzed to determine its significance for the current literature review. When cited references met the above criteria but were not in the initial PubMed search results, they were included as well.

WHO SHOULD BE OFFERED SURGICAL RISK REDUCTION?

All surgical procedures carry an inherent level of risk. In risk-reduction surgery, a woman decides to undergo an elective mastectomy on a breast without pathologic abnormalities. The patient must have an accurate understanding of the

potential benefits, risks, and alternatives. This decision is a difficult one and necessitates a thorough understanding of the diagnosis, prognosis, morbidity, mortality, and the potential risks and benefits associated with treatment. The effect of reducing, not completely eliminating, the risk of breast cancer must outweigh the potential drawbacks of surgery.

Primary Prevention: Bilateral Risk-Reduction Mastectomy

The goal of bilateral risk-reduction mastectomy is to reduce the incidence of breast cancer in certain high-risk patients. To determine objective risk stratification, a complicated mix of familial and genetic factors, reproductive history, lifestyle options, and history of certain abnormality found on breast biopsies must be taken into account. Patients are provided information about the benefits and risks with regard to risk-reduction surgery. Rather than perform risk-reduction mastectomy for reason of speculative benefit, attention is now being directed toward establishing evidence-based data showing objective benefits for women demonstrated to be at elevated risks.

Initial stratification determines which patients should undergo further evaluation in addition to normal a history and physical examination. In the past, risk-reduction mastectomy had been performed for women with any family history, painful breasts, cancer phobia, or history of multiple breast biopsies. With significant advances in genetic screening and understanding of the molecular characteristics of breast abnormality, the current trend is to quantify risk and assess accordingly.

In a woman without a personal history of breast cancer, familial and genetic factors should be evaluated first. A full family history should be obtained, specifically discussing breast and ovarian abnormality. A formal referral to a genetic counseling specialist should be made if a patient has elevated risk based on family history. Further analysis for known genetic mutations such as the BRCA 1/2 (hereditary breast and ovarian cancer), TP53 (Li-Fraumeni syndrome), STK11 (Peutz-Jegher syndrome), PTEN (Cowden syndrome), and CDH1 (hereditary diffuse gastric cancer) genes may be assessed.[4]

Multiple characteristics obtained during routine patient evaluation may indicate increased risk for breast cancer. Elevated levels of estrogens are associated with increased risk of breast cancer. Nulliparity, increased time between menarche and age of first live birth, and use of hormone therapy for treatment of the symptoms of menopause all increase risk. Furthermore, elevated body mass index, alcohol consumption, and tobacco consumption have all been associated with increased risks of breast cancer development.[5] Last, women with a history of radiation therapy to the chest before age 30 are at elevated risk for the development of breast cancer.[6]

With the growing understanding of the myriad risk factors, both modifiable and innate, more information about quantifying individual patient risks is possible. Much research has sought to quantify individual risk factors and attribute scores to categorize patients into risk levels. The 2 most commonly used scoring systems are those modified from the Gail and Claus models.

The 1989 publication from Gail and colleagues[7] quantified the risk of developing breast cancer for groups of Caucasian women either under or over 50 years of age. A risk score was determined using age at menarche, age at first live birth, number of previous breast biopsies, and number of first-degree relatives with breast cancer. With the progress of genetic screening, specifics of molecular abnormality, and modifiable risk factors, multiple models have been proposed to most accurately assess individual risk. The National Cancer Institute's Breast Cancer Risk Assessment Tool is a risk calculator based on an updated Gail model. It assesses a 5-year and lifetime risk score for women 35 years of age and older. It attempts to assess risk for multiple races of women and also addresses patient age, age at menarche, age at first live birth, number of first-degree relatives with breast cancer, number of previous breast biopsies, presence of atypical ductal hyperplasia on biopsy, race, mutation in BRCA 1/2 genes or other syndrome associated with increased breast cancer risk, history of ductal or lobular carcinoma in situ, and previous chest radiation for Hodgkin lymphoma.[8,9] The contemporary Gail score continues to be important because US Food and Drug Administration guidelines for recommending discussion about surgical risk prevention and chemoprophylaxis are based on Gail score values.

We are still not able to predict who will get breast cancer and who will succumb to breast cancer regardless of risk factors. Further complicating matters is that the medical and surgical treatment of breast cancer has evolved significantly. In the 1990s, Ernster[10] demonstrated that among certain high-risk patients, most of the women would not die from breast cancer. In the early 2000s, Roukas[11] noted the incomplete penetrance of the BRCA mutation, at that time showing that 70% of gene carriers were affected. This data postulated that up to 30% do not have genetic penetrance and thus risk-reduction mastectomy

would not be therapeutic. As diagnosis and treatment change, data reflecting incidence and mortality change as well.

In most practices, following the recommendations of the National Comprehensive Cancer Network (NCCN), the option of risk-reduction surgery is presented to patients with BRCA 1/2 or other predisposing gene mutation, strong family history of breast cancer, high-risk breast lesions like lobular carcinoma in situ (LCIS)/atypical ductal hyperplasia (ADH), or breasts difficult to survey.[4,12] Multiple studies have shown a decrease in breast cancer incidence after bilateral risk-reduction mastectomy for both high-risk and moderate-risk women.[13–15] In addition, many have shown a disease-specific morality decrease after risk-reduction surgery in this patient population.[16–18] Further interpretation can extrapolate that 6 women at high risk need to undergo a risk-reduction mastectomy to prevent one case of breast cancer, and that 25 women at high risk would need to be treated to prevent one breast cancer death.[19]

Although objective and quantifiable data are useful in making medical and surgical decisions, the psychological effect of confronting breast cancer must be taken into account. A woman who has seen a family member or friend struggle with breast cancer faces a looming cloud of uncertainty regarding how the disease may or may not affect her. As risk factors become known and risk score validity increases, a feeling of inevitable threat can profoundly impact patients' lives. A patient's understanding of her individual risk can be a large contributor to psychological health. Van Dijk and colleagues[20] noted a significant decrease in perceived risk among women after counseling. Before education, most women believed they have risks much higher than their actual risk. This overestimation of risk was particularly significant for women at low risk, a population less likely to benefit from risk-reduction surgery. The discrepancy between actual and perceived risk is relevant in light of multiple studies showing that many women considering risk-reduction surgery made decisions based on an incorrect actual level of actual risk.[21,22] Physician counseling is paramount in providing patients with all available information working together to determine appropriate treatment goals.

Recurrence Prevention: Contralateral Risk-Reduction Mastectomy

The goal of contralateral risk-reduction mastectomy is to reduce the risk of developing breast cancer in the contralateral breast of a woman previously diagnosed with unilateral breast cancer. Women with a personal history of carcinoma in one breast have an estimated risk of 0.5% to 1% per year of contralateral breast cancer.[23,24] Although most data show contralateral risk-reduction mastectomy does decrease the incidence of contralateral breast cancer,[25] insufficient evidence is present to show a decrease in breast cancer–specific mortality.[24,25] Mortality is often dictated by metastasis of the index tumor. No improvement in disease-specific mortality is seen if the risk of mortality from metastasis of the index tumor is greater than the added mortality risk from contralateral breast cancer. The merits of the contralateral risk-reduction mastectomy are then based on the physical and emotional sequelae of diagnosis and treatment of a second cancer, not based on prolonging life.

A woman with a BRCA mutation has 56% to 87% lifetime risk of developing breast cancer. In a patient with unilateral breast cancer and a BRCA mutation, there is a 40% to 50% risk of developing a second primary breast cancer in the contralateral breast. It is generally accepted that options for contralateral risk-reduction mastectomy should be presented to women at high risk for contralateral breast cancer based on adaptations from the Society of Surgical Oncology's recommendations. This group of women is characterized by having age at diagnosis less than 40 years, lobular histology of the primary breast cancer, strong family history, contralateral breast benign findings, difficult surveillance, reconstruction considerations, or genetic findings discovered after initial mastectomy.[26–28] Barry and colleagues[27] have also demonstrated multivariate analysis identifying invasive lobular histology, an ipsilateral multicentric tumor, and a 5-year Gail risk 1.67% as predictors of a contralateral malignancy.

After an initial breast cancer diagnosis, it is reasonable for a woman to have psychological anxiety related toward the possibility of developing breast cancer in the unaffected breast. In comparison to the psychological effects previously addressed regarding women who may pursue a bilateral risk-reduction mastectomy, women with unilateral breast cancer also have to assess the risks and benefits of operating on a breast without known abnormality. Where these patients differ is that they already have had one cancer diagnosis and are faced with the sequelae of neoadjuvant and adjuvant treatment. It can be daunting to imagine a second cancer diagnosis in the future and the thought of having to undergo treatment again. The fear of possible future cancer in the other breast potentially could sway a woman to pursue more operative intervention upfront in the hopes of avoiding a second breast cancer diagnosis.

What is clear is that women who thought they had an active role in decision making were twice as likely to be satisfied with contralateral prophylactic mastectomy when compared with patients who thought they were guided toward a decision or shared the decision-making process with the physician.[29]

SHOULD LYMPH NODES BE ASSESSED?

In evaluating a breast without evidence of breast cancer, it is assumed that the ipsilateral lymph nodes would also be free of abnormality. It is known, however, that there is a chance of discovering occult abnormality in what was thought to be benign breast tissue. In women undergoing contralateral risk-reduction surgery with a family history of breast cancer, occult malignancy is found in 5% to 15% of patients.[30] The implications of finding occult disease include the need to assess the axilla for metastases. A sentinel lymph node assessment during the initial procedure could have profound effects on any further necessary operative and medical intervention. In women choosing to pursue a risk-reduction mastectomy, the benefits and risks of axillary lymph node sampling should be addressed.

It is generally accepted that an intact breast is required for a sentinel lymph node biopsy to be of value. Proponents of upfront sampling believe if it is not done initially, it cannot be done later. Removing the normal lymphatic pathway alters the drainage system that would otherwise give an indication of tumor spread. A sentinel lymph node biopsy performed upfront could also obviate returning to the operating room for axillary staging were occult abnormality to be found. In addition, a negative sentinel lymph evaluation could forgo the need for a second procedure that would be required if an occult malignancy was found.

With a lack of index tumor, as all risk-reduction surgery presumes, no generalized standard for routine assessment of the lymph node basin has been proven beneficial. Instead, many propose a surveillance approach. Sentinel lymph node biopsy can be safely omitted in patients who are undergoing a bilateral risk-reduction surgery or contralateral risk-reduction surgery when the known malignancy is at an early stage. Evidence suggesting some possible benefit for sentinel lymph node sampling is found in women undergoing contralateral risk-reduction surgery with known malignancy being locally advanced, inflammatory, or recurrent.[12]

No official NCCN standard has been established regarding the sampling of lymph nodes in risk-reduction surgery. Guidelines are recommended for those at high risk for occult abnormality. Sampling may be indicated in women choosing bilateral risk-reduction surgery who have either had abnormal imaging and no biopsy or who have strong family history and no previous imaging.[4]

WHAT ARE THE INDICATIONS FOR NIPPLE-AREOLA–SPARING MASTECTOMY?

There is considerable evidence showing improved cosmetic results and patient-reported outcomes from reconstruction after nipple-areola complex–sparing mastectomy.[31] With improved technical advances allowing for complete mastectomy without jeopardizing the mastectomy flaps and nipple areolar complex, there is need to determine for which patients the technique is oncologically safe. A literature review by Mallon and colleagues[31] explored the rate of malignancies discovered in the nipple in women undergoing mastectomy. A wide range of results, from 0% to 53%, was found when using data irrespective of tumor size, distance from the nipple, and specific tumor abnormality. Mounting evidence has shown that an oncologically sound procedure is possible if certain criteria are followed. Although some breast tissue may be left behind in a nipple-sparing mastectomy, the risk for certain patients for subsequent development of breast cancer is acceptably low.

It is generally agreed that nipple-areola complex–sparing mastectomy can be offered to women with certain tumor characteristics, ensuring the results are oncologically equivalent to traditional mastectomy techniques. Characteristics often included are solitary or multifocal tumors $\leq$3 cm, tumor at least 2 cm from the nipple, and no evidence of abnormality on retroareolar sampling. These values come from data showing minimal to near zero involvement of the nipple when the tumor is at least 2 to 4 cm from the nipple[32,33] and from data showing a significant increase in occult tumors found in tumors larger than 2 cm when compared with tumors smaller than 2 cm.[32,34,35] In addition, approximately 30% of multicentric tumors have been associated with involvement of the nipple.[31] Certain tumor characteristics and genetics are associated with increased nipple involvement. Tumors with lymphovascular invasion, HER2 gene amplification, and negative hormone receptor status all increase the likelihood of nipple involvement.[31]

Critics of nipple-sparing mastectomy point to a dearth of prospective and long-term data. Nipple-areola–sparing mastectomy does leave behind terminal duct lobular units when compared with simple mastectomy or skin-sparing mastectomy.

However, the clinical consequence of this is uncertain. It is estimated that only 1% of tumor recurrences after nipple-areola–sparing mastectomy occur under the nipple areolar complex.[36]

Nipple-sparing mastectomy should be offered to select patients who will benefit from oncologically appropriate treatment and optimally aesthetic reconstructive options. Those patients for whom nipple-sparing mastectomy is not appropriate require further surgery to achieve appropriate surgical treatment of breast cancer. Technical improvements continue to decrease the complications of nipple-sparing mastectomy. With low complication rates and comparable local recurrence rates, the benefits of nipple-sparing mastectomy, for suitable patients, will likely continue the advances in aesthetic breast reconstruction.

THE AUTHORS' PERSONAL APPROACH FOR BREAST RECONSTRUCTION AFTER RISK-REDUCTION MASTECTOMY

It is very important for the patient to feel empowered by education and information so that they feel they are in control of their decision-making process. More understanding and appropriate counseling leads to improved long-term satisfaction. The authors' personal approach for breast reconstruction after risk-reduction mastectomy is to educate regarding individual risk, discuss the ramifications of all reconstructive options, and explore a patient's psychological viewpoint on this choice. Most patients have fears and anxieties that need to be discussed openly. Open discussions between the physician and patient often aid in tailoring the surgical plan and allow for a more informed decision. For patients with breast cancer that are deciding on a contralateral risk-reduction mastectomy, a particularly important area of discussion is the potential need for long-term surveillance. For some patients, preserving their natural breast, especially when sensation is considered, is more important than the anxiety that they may have before annual radiographic testing. In contrast, other patients find the anxiety of continued surveillance difficult to deal with and may therefore decide to proceed with the contralateral risk-reduction mastectomy. This option essentially eliminates further mammographic follow-up. Although operative times may be extended, the perioperative recovery process is not much longer for bilateral compared with unilateral reconstruction. For certain patients, this information can be instrumental in making an educated decision regarding options. Another important consideration for these patients, specifically when autologous abdominally based breast reconstruction is preferred, is to explain that certain donor sites can only be used once and cannot be saved for later. Using the abdominal donor site for a unilateral reconstruction precludes use of the same donor site for any subsequent reconstruction on the contralateral side. If a situation were to arise when a contralateral mastectomy was required, an alternative type of reconstruction would be required.

In cases of bilateral risk-reduction mastectomy for genetic reasons, the decision to undergo this elective procedure is a difficult one. The patients are often young women whose aesthetic considerations play a major role in their decision-making process. It is comforting to be able to offer these patients a nipple-preserving mastectomy using an inframammary incision, an option in which the scar is nearly hidden in an inconspicuous location. The result can be a very natural breast reconstruction without scars on the visible part of the breast. The ability to potentially perform a breast reconstruction with little, if any, obvious external sequelae may make the decision-making process easier, knowing that excellent cosmetic results are possible. Both autologous and implant-based reconstructions are discussed. Specific care must be addressed toward total body aesthetics with the goal of preserving each patient's sense of femininity, and it is hoped, serving to ease the burden of this genetic predilection.

DISCUSSION

Current Status of Evidence for Risk-Reduction Mastectomy

Breast cancer affects nearly every woman either personally or through a family member or friend. With advances in genetic screening, risk factors, and tumor-specific abnormality, more information about risks for developing cancer and prognosis is available. Correspondingly, physicians and patients are seeking both surgical and nonsurgical means to reduce the incidence and disease-specific mortality of breast cancer. Risk-reduction surgery has become more common as the ability to objectively assess risk has improved. In addition, breast reconstruction advances may make the sequela of cancer prevention and treatment slightly less burdensome.

1. Bilateral risk-reduction surgery has been shown to both decrease the incidence of breast cancer and improve overall disease-specific survival. It should be offered to women who have been determined to be objectively at high risk for developing breast cancer.

2. Contralateral risk-reduction surgery has been shown to decrease the incidence of contralateral cancer. Insufficient evidence demonstrates an improvement in overall disease-specific survival. It should be offered to women who require mastectomy for a known cancer and who will benefit from the elective removal of a contralateral breast without known abnormality.
3. It is imperative for patients to understand their individual risks of developing breast cancer. Appropriately selected patients should be educated sufficiently to be able to make decisions that correspond with their individual goals. An overestimation or underestimation of risk does a disservice to a woman faced with tough choices. Patient-reported outcomes are highest when patients feel educated by the entire medical team and allowed to make a decision that fits within their goals.
4. Specific data are still lacking regarding the indications for sampling lymph nodes in breasts without known abnormality. However, in certain women with high risk for occult abnormality, data do lean toward recommending sampling. For this group, the ability to have already staged the axilla when occult abnormality is found must be weighed against possible morbidity.
5. Guidelines for the appropriateness of nipple-areola complex–sparing mastectomy are evolving. Patient-reported outcomes for both aesthetics and psychosocial well-being are higher with reconstruction after nipple-areola complex sparing mastectomy. In accordance, the boundaries should be pushed while making sure oncologically appropriate surgery is still being performed.

FUTURE DIRECTIONS FOR IMPROVING CLINICAL CARE

As genetic screening becomes more prevalent and more is learned about the specific behavior of individual tumors, more information regarding risks and prognosis becomes clear. As both surgical and nonsurgical means of risk reduction improve, it becomes even more important to determine which patients will benefit from certain interventions. With this in mind, objective and quantifiable data must be available to assist patients in making informed decisions. No surgical or medical intervention exists without risks. The more informed and involved patients are, the more satisfied they are with the decision and outcomes.

Although a large, blinded, well-executed, randomized control trial would be the ideal means to generate data, it is unlikely that this is feasible. Future research will generate more long-term data and continue to explore the possible confounding variables that could influence data. Differences in age, race, genetic makeup, and tumor specifics should all be accounted for and used in risk calculation. Qualitative data regarding patient-reported outcomes also will serve to educate women in their decision-making processes.

SUMMARY

Risk-reduction mastectomy has become more common, safe, and accepted for women with elevated risk of developing breast cancer. Although the incidence of breast cancer has declined in women who undergo both bilateral and contralateral risk-reduction surgery, the improvement in mortality for the contralateral risk-reduction surgery has not been demonstrated. Appropriately risk-stratified women ought to be educated regarding their individual risk in order to make an informed decision. In conjunction with the advancements of nonsurgical treatment of breast cancer, understanding the possibilities of reconstruction continues to grow.

As more is learned and techniques progress, the relative merits of surgical risk reduction will likely change as well. With improved results, decreased donor site morbidity, and an understanding of total body aesthetics, the burden of this difficult decision-making process is slowly diminished.

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