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Prophylactic Mastectomy and Inherited Predisposition to Breast Carcinoma

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Relative to her risk of breast carcinoma, the woman with a *BRCA1* or *BRCA2* gene mutation can be managed either by intensive screening (with or without chemoprevention) or by prophylactic mastectomy. Although it would be preferable to avoid prophylactic surgery, the current level of screening technology and the rudimentary state of chemoprevention do not guarantee a good outcome with intensive surveillance. A review of the currently available data was undertaken to determine the efficacy of prophylactic surgery, intensive screening, and chemoprevention. An attempt then was made to extrapolate the efficacy of the various approaches to the management of women who carry *BRCA1* or *BRCA2* gene mutations. Intensive surveillance may not detect breast carcinoma at an early, curable stage in young women with *BRCA1* or *BRCA2* gene mutations because the growth rate of the tumors in these women most likely will be rapid and the density of the breast tissue may compromise detection. Chemoprevention is in its infancy, and its efficacy in this population is unknown. Conversely, prophylactic surgery may not be completely effective in preventing breast carcinoma. The authors are hopeful that sometime in the next decade advances in chemoprevention, screening technology, or breast carcinoma treatment will make mastectomy obsolete. However, for the time being prophylactic mastectomy has attributes that make it an alternative for this population that must be considered. Careful discussion of all options is essential in the management of these women. ***Cancer*** **1999;86:2502–16.**
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The cloning of the *BRCA1* and *BRCA2* genes has opened the door to the identification of a subset of women at a very high risk of developing breast or ovarian carcinoma.[1] To develop clinical management strategies, it is important to understand the genetic issues, including the frequency and penetrance of the gene mutation and the expected age at which that malignancy will develop. In general, women with a *BRCA1* mutation are believed to have a 19.1% risk of developing breast carcinoma by the age of 40 years, an 85% risk of developing breast carcinoma by the age of 70 years, and between a 26–85% risk of developing ovarian carcinoma by the age of 70 years.[1-4] Women with a BRCA2 mutation are believed to have a risk of developing breast carcinoma similar to that of women with a *BRCA1* mutation, although perhaps beginning at a later age,[2,5] and a 10–16% risk of developing ovarian carcinoma by the age of 70 years.[2,6]

The currently available management strategies are limited, and prophylactic mastectomy has reemerged as a reasonable option in these high risk patients (Fig. 1). To determine the efficacy and advis-

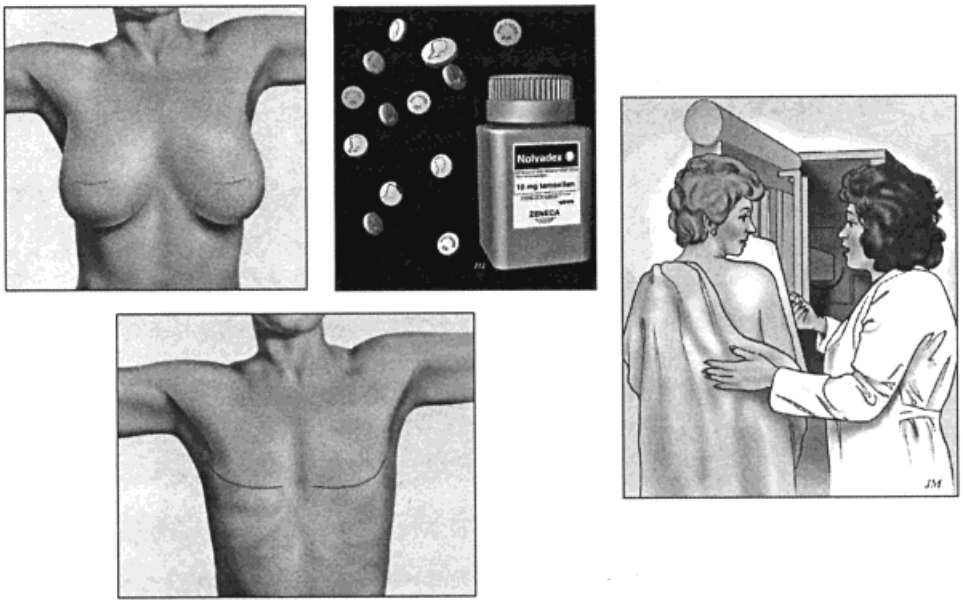

FIGURE 1. Options for a mutation carrier. Relative to her risk for the development of breast carcinoma, a woman found to harbor a mutation in the *BRCA1* and/or *BRCA2* genes can be managed by intensive observation (with or without chemoprevention) or by prophylactic mastectomy, with or without reconstruction.

ability of prophylactic surgery, that option must be compared with the efficacy of the currently available alternatives: screening and chemoprevention.

In the past, prophylactic mastectomy frequently was used for patients who would not be considered at high risk today. Given the fact that surgeons tended to use what currently would be considered an inadequate procedure (subcutaneous mastectomy) and the fact that reconstruction was rudimentary, it is not surprising that this procedure fell out of favor. Current-day prophylactic mastectomy involves using the appropriate procedure (total mastectomy) and continuously improving reconstruction methods to deal with a group of patients at proven high risk (proven carriers of *BRCA1* and *BRCA2* gene mutations). These current techniques and indications must be compared objectively with the current efficacy of screening and the emerging field of chemoprevention. In this comparison, prophylactic mastectomy appears at least as reasonable, and at times more appropriate, than the alternatives. In the future, as chemoprevention becomes more effective and as screening technologies improve, the need for prophylactic mastectomy may disappear.

Breast carcinoma screening is justified in the general population, most likely after the age of 40 years, and certainly after the age of 50 years.[7] Intensive screening of carriers of *BRCA1* and *BRCA2* gene mutations is likely to be indicated and effective if initiated at an early age,[5] but even with the current technology advanced breast carcinoma still will develop in a certain number of women who will die despite intensive screening. Chemoprevention of breast carcinoma is in its infancy and although the Breast Cancer Prevention Trial has shown promise by suggesting that tamoxifen may decrease the risk of breast carcinoma, to date no data have proven that tamoxifen will be effective for carriers of *BRCA1* and *BRCA2* gene mutations. Therefore, both screening and chemoprevention must be compared with removal of breast tissue by prophylactic mastectomy as options for treatment, given that prophylactic mastectomy appears to reduce the occurrence of breast carcinoma without providing absolute control.

To evaluate each approach with respect to carriers of *BRCA1* and *BRCA2* gene mutations, our method has been to assess the risk and benefits through a series of questions, including: Is effective chemoprevention available? What is the efficacy of screening? With screening, how often will breast carcinoma be identified at an early, curable stage? What is the efficacy of prophylactic mastectomy? How often will breast carcinoma develop in women who have undergone prophylactic mastectomy, and how many of those women will die? What type of mastectomy should be performed? When should this surgery be performed? Should the patient undergo reconstruction, and if so, what type? What will be the psychosocial effect of this procedure on the patient and her family?

We will attempt to summarize the state of the art as it relates to these questions for chemoprevention, screening, and prophylactic mastectomy. Many of these issues cannot be answered at our current level of knowledge, particularly with respect to the value of chemoprevention, and continued research is essential.

Chemoprevention

Chemoprevention is defined as the utilization of a drug or a chemical to prevent the development of cancer. Whereas this approach may be ideal in the future, to our knowledge no proven agent currently is available. The Breast Cancer Prevention Trial has suggested that tamoxifen is effective in preventing breast carcinoma. However, it is unclear whether tamoxifen will be effective in the population carrying a *BRCA1* or *BRCA2* gene mutation or at what age tamoxifen treatment should be initiated, how long it should be continued, or what the long term effects will be. It will be many years before the extended use of this or any agent has been tested in a young population.

Screening

Intensive screening programs are predicated on the current ability to provide adequate treatment when breast carcinoma is detected. Effective surveillance therefore is dependent on an adequate incidence of breast carcinoma, a silent early phase, adequate treatment, and adequate technology.[8] Because screening would appear to be a much less distressing and mutilating approach, it is tempting to recommend intensive screening rather than prophylactic mastectomy to the woman who carries a *BRCA1* or a BRCA2 gene mutation. However, it is important to remember that intensive screening does not work by preventing breast carcinoma (primary prevention), but rather works by detecting breast carcinoma at an earlier, more treatable stage (secondary prevention). The efficacy of intensive screening is dependent on the ability to detect breast carcinoma early enough so that surgery, chemotherapy, or radiation (or a combination of all three) may be used to eradicate the tumor. If cure rates were not stage-dependent, then early detection would not be necessary.

To our knowledge the efficacy of screening for a woman who carries a *BRCA1* or *BRCA2* gene mutation has not been tested. Although to our knowledge no data specific to *BRCA1* and *BRCA2* carriers are available, it is possible to make some broad predictions relative to this group using the findings in the general population as a baseline.

Screening is effective in women age >50 years because they have an adequate incidence of breast carcinoma development,[9] because of the existence of a silent, early phase of breast carcinoma that is detectable by mammography,[9] because adequate treatment is available for women with breast carcinoma (the decreased mortality found with screening in the randomized trials of women age >50 years is dependent on the ability to cure this disease, and the cure is greater at a lower stage), and because the current technology is adequate to detect breast carcinoma in women age >50 years.

The silent, early phase of breast carcinoma presents a window of opportunity in the postmenopausal woman because it is at this stage that a tumor can be identified on mammography even before it reaches a palpable size. This time can range from 1–3 years, in part due to the doubling time of tumors in this age group. Assuming that a single tumor begins the process of carcinogenesis, volume calculations show that 20 doublings will need to take place for the tumor to reach a greatest dimension of 1 mm, and 10 more doublings will need to take place for the tumor to progress to a greatest dimension of 1 cm.[10,11]

The threshold size for detecting breast tumors by mammography is approximately 1–2 mm (approximately 20 doublings), whereas the threshold size for detecting breast tumors by palpation is approximately 1 cm (approximately 30 doublings). Spratt et al.[10,11] have estimated a doubling time of 103–191 days for lymph node negative invasive tumors in women age >50 years. Using an estimate of 125 days and using volume calculations, the time from inception to mammographic detection would be approximately 2500 days (6.8 years), and the time from mammographic detection to clinical detection by palpation would be an additional 1250 days (3.4 years) (Fig. 2). This produces a window of opportunity of >3 years during which time breast tumors will be detectable by mammography but not by palpation. In general, the longer this window is, the more effective screening mammography will be. In addition, the majority of women go through a phase of ductal carcinoma in situ before the development of invasive breast carcinoma, which adds to the window of opportunity.

Efficacy of Surveillance in Patients with Hereditary Breast Carcinoma

Breast carcinoma will develop in as many as 19.1% of female carriers of *BRCA1* and *BRCA2* gene mutations by the age of 40 years, and in as many as 50% of these women by the age of 50 years.[1-4] Two factors will have a negative effect on the length of the mammographic detection window in this population. First, the rate of growth of breast carcinoma is faster in younger women and second, the breast parenchyma is denser in younger women, making mammographic detection more difficult.

Spratt et al.[10,11] have estimated a doubling time of 50–64 days for lymph node negative invasive tumors in women in their 30s. Using 50 days, and assuming the same mammographic and palpation thresholds discussed earlier, the time from inception to mammo-

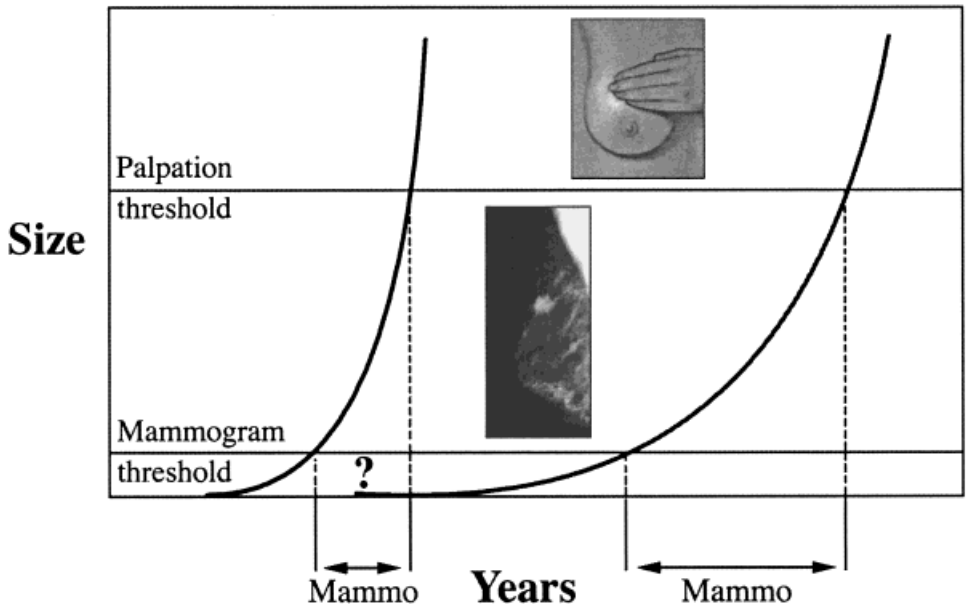

FIGURE 2. Doubling time of 50 days versus 125 days. In postmenopausal women, the growth rate of tumors is slower, depicted here by a doubling time of 125 days, and the window of time for mammographic detection (mammo) is relatively long. In premenopausal women the growth rate of tumors is faster, and the window of time for mammographic detection is shortened.

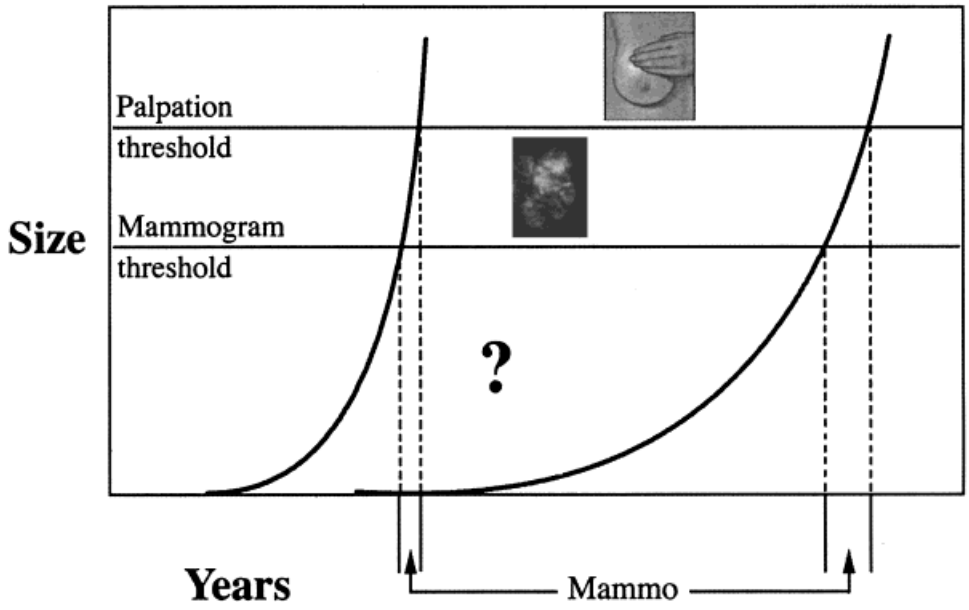

FIGURE 3. Dense breast tissue. In premenopausal women, the density of breast tissue increases the mammographic threshold and also can shorten the window of time for mammographic detection (mammo).

graphic detection would be approximately 1000 days (2.7 years), and the time from mammographic detection to clinical detection by palpation would be an additional 500 days (1.35 years) (Fig. 2). This produces a window of slightly greater than 1 year during which breast tumors will be detectable by mammography, but not by palpation.

However, another problem is that young women tend to have denser breast tissue and therefore the ability to visualize tumors on mammograms is diminished and the ability to palpate tumors is compromised (Fig. 3). In fact, Dr. Barbara Smith found negative results on mammography in >100 women who were age <40 years and underwent treatment for breast carcinoma at the Massachusetts General Hospital (personal communication). This finding means that the mammographic and palpation thresholds most likely are larger in the younger population and that as many as 33% of the tumors in this group may not be detectable by mammography.

Carriers of the *BRCA1* and *BRCA2* gene mutations may or may not have denser breast tissue on mammography than noncarriers, but it would appear reasonable to assume that the density of breast tissue is commensurate with age.

With regard to the rate of tumor growth, it is likely

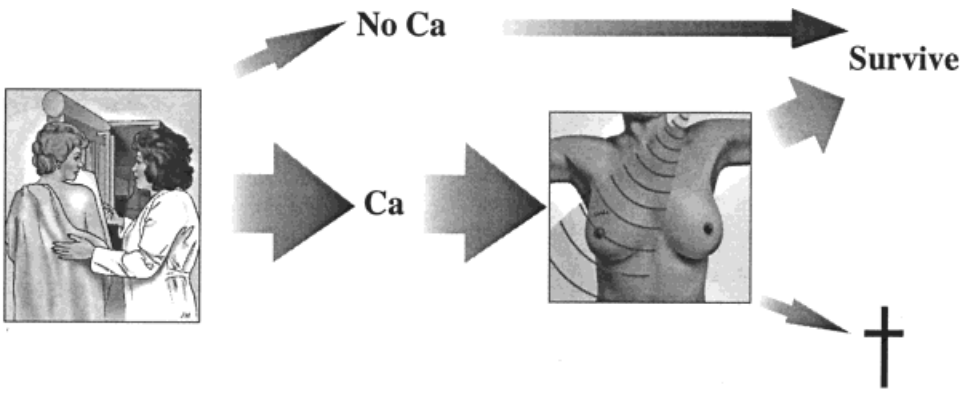

FIGURE 4. Possible outcomes of breast screening. If all women carrying mutations in the *BRCA1* and *BRCA2* genes are screened, the level of the current technology will allow the majority of tumors to be detected at a stage when the carcinoma (ca) still is curable. In the postmenopausal patient, approximately 80–90% of patients screened can be cured. In this premenopausal group, with dense breast tissue and fast-growing tumors, the number of tumors detected when curable most likely will be <80%. This fact must be taken into account when recommending screening to this group. The size of the arrows is a visual representation of the number of patients expected to move down each pathway. The exact size of the arrows will be determined by future research.

that tumors in carriers of the *BRCA1* gene mutation will grow rapidly both because of younger age and the gene mutation. Foulkes et al.[12] found that Ashkenazi Jewish women who carry one of the two established mutations (185 delAG and 5382insC) were more likely to have Grade 3 tumors (11 of 12 tumors were Grade 3 in carriers vs. 29 of 100 tumors in noncarriers), were more likely to be lymph node positive (45.5% in carriers vs. 31.1% in noncarriers), and were more likely to have tumors that were larger in greatest dimension (mean size 2.48 cm in carriers vs. 1.71 cm in noncarriers). Other studies found that tumors in carriers were more likely to be estrogen receptor negative[13,14] and p53 positive.[15] Therefore, carriers of the *BRCA1* mutation will likely have faster-growing tumors that will pass through the mammographic window rapidly. BRCA2 breast tumors also appear to be of higher grade than sporadic tumor and are also likely to grow faster and be less easily identified when small.[16]

Therefore, we would expect that the carriers of *BRCA1* and *BRCA2* gene mutations will have rapidly growing tumors that will be difficult to identify by mammography or palpation, especially when the patients are age <40 years. Despite intensive screening with our current technology, we can expect to detect these tumors later and at a larger size. It is reasonable to assume that a certain number of tumors will have metastasized by the time they are detected.

Regardless of growth rate, screening will not be effective if there is poor compliance with screening recommendations. Lermann found that among women who carried a *BRCA1* or *BRCA2* gene mutation, <50% followed the recommendations for mammography when evaluated 6 months after testing.[17] In the absence of compliance, screening will be ineffective.

Possible Outcomes of Screening

The possible outcomes of screening are depicted in Figure 4. If all women carrying gene mutations in *BRCA1* and *BRCA2* receive a recommendation for intensive screening, the current technology will permit detection of tumors at a still curable stage in the majority of these women. Approximately 80–90% of the screened patients can be cured[18] in the postmenopausal stage, whereas the number of tumors detected at a still curable stage most likely will be much lower in the premenopausal group, who have dense breast tissue, fast-growing tumors, and possibly poor compliance. The size of the arrows shown in Figure 4 are roughly proportional to the number of women predicted to go along each path, and the proportions will change as we increase our understanding of the natural history and treatment of those patients (Fig. 4). The number of women who develop breast carcinoma will be decreased when adequate chemoprevention becomes available. The number of women who are cured of breast carcinoma will increase with better screening technology (detecting tumors at an earlier stage) and improved treatment (more breast carcinoma cured stage for stage).

PROPHYLACTIC SURGERY TO REDUCE THE RISK OF BREAST CARCINOMA

The promise of chemoprevention not withstanding, prophylactic mastectomy is the only currently available method that appears to decrease the lifetime risk of breast carcinoma to a significant degree, but mastectomy also is clearly the most invasive of the treatment options. Efficacy is dependent on the ability to remove nearly all breast tissue and on the supposition that the risk of tumor is proportional to the amount of residual breast tissue. Although prophylactic mastectomy is a disfiguring approach that many in the med-

TABLE 1
Series and Case Reports of Prophylactic Mastectomy in the Literature[a]

Author	Cases	Denominator	Mastectomy	Time to breast carcinoma	Mean follow-up	Breast carcinoma developed	Reference
Case reports							
Holleb et al.	2	?	Total	10 years, 12 years		Flap, flap	19
Ziegler and Kroll.	1	?	Total	18 years		Flap	20
Goodnight et al.	1[b]	?	Subcutaneous	3 years		Flap	21
Bowers and Radlauer	2	?	Subcutaneous	3 years, 10 years	NA	Flap, flap	22
Mendez-Fernandez et al.	1	?	Subcutaneous	8 years	NA	Nipple	23
Eldar et al.	1	?	Subcutaneous	6 years	NA	Flap	24
Jameson et al.	1	?	Subcutaneous	42 years	NA	Under nipple	25
Series							
Humphrey	3	16	Subcutaneous	NA	NA	Flap	26
Pennisi and Capozzi	6	1232[c]	Subcutaneous	NA	NA	Unknown	27
Woods and Meland	5	1500	Subcutaneous	NA	22 years	Unknown	28
Slade	1	83[d]	Subcutaneous	10 years	NA	Under nipple	29
Fredericks	1	39[e]	Subcutaneous	5 years	NA	Flap	30
Amaaki et al.	1	9[f]	Subcutaneous	NA	NA	NA	31
Hartmann et al.	7	950	89% subcutaneous	17 years	NA	NA	32

NA: not available.

[a] Patients were excluded as not truly prophylactic if they had contralateral or ipsilateral breast carcinoma at the time of the initial procedure.

[b] Three patients were excluded because of breast carcinoma at the time of the initial procedure.

[c] Two hundred sixty-eight patients were excluded because of breast carcinoma at the time of the initial procedure.

[d] Five patients were excluded because of breast carcinoma at the time of the initial procedure.

[e] One patient was excluded because of breast carcinoma at the time of the initial procedure.

[f] Eight patients were excluded because of breast carcinoma at the time of the initial procedure.

ical profession would prefer to avoid, it must be compared objectively with screening and chemoprevention in terms of the ultimate result.

The perception exists that the literature has called into question the efficacy of prophylactic mastectomy (based primarily on reports suggesting failure of the procedure to eliminate the risk of breast carcinoma[19-32]). Although at first glance the literature[19-32] (Table 1) would appear to suggest that prophylactic mastectomy is not completely effective, in actuality the efficacy of prophylactic mastectomy has not been studied adequately. Although several series and case reports appear in the literature, the combined data do not provide a compelling argument for or against this procedure. In addition, the method of resecting breast tissue and the indications for prophylactic mastectomy have been quite variable and might lead to a false assessment of its efficacy. Confounding factors within these reports include: 1) the type of mastectomy performed, 2) technical thoroughness of the mastectomy, 3) the indications for prophylactic mastectomy, 4) limited patient follow-up, and 5) lack of a denominator for adequate comparison with a population not undergoing this procedure.

To understand the important association between the type of mastectomy performed and the efficacy of prophylactic mastectomy, it is essential that the technical differences and resulting residual tissue be discussed. Removal of all breast tissue most likely is not possible, but the extent of residual tissue is dependent on the procedure performed and the meticulousness of the technique.

The most extensive mastectomy is the radical mastectomy, which involves removal of the nipple-areolar complex and surrounding skin, "all" breast tissue, the pectoralis major and minor muscles, and the axillary lymph nodes. Even with a radical mastectomy, some breast tissue remains, and new primary breast tumors can develop.[33] The radical mastectomy is a deforming procedure that makes reconstruction difficult, and it has no role in prophylactic surgery.

The modified radical mastectomy involves removal of the nipple-areolar complex and surrounding skin, "all" breast tissue, and the axillary lymph nodes but does not include removal of the pectoralis major muscle. The modified radical mastectomy is really not necessary for prophylactic surgery because formal dissection of the lymph nodes adds morbidity without increasing the efficacy of the procedure. Some surgeons believe that removing the lymph nodes is necessary to ensure total removal of the breast tissue contained in the tail of Spence, but more likely than not this area is removed using a technical total mastectomy.

The total or simple mastectomy removes the nip-

ple-areolar complex and surrounding skin and "all" breast tissue, but does not include removal of the axillary lymph nodes or the pectoralis major and minor muscles. This is the surgery most often performed for prophylactic surgery today.

The subcutaneous mastectomy removes only the breast tissue that is separate from the nipple, but does not include removal of the nipple-areolar complex, the skin of the breast, the axillary lymph nodes, or the pectoralis major and minor muscles. The subcutaneous mastectomy is performed through an incision made in the inframammary crease. Dissection then is performed by separation of the skin and nipple from the breast tissue. It technically is difficult to produce thin flaps and to remove the breast tissue found in the tail of Spence, thereby allowing breast tissue to be left behind in this area. In addition, by definition, the nipple and its underlying breast tissue are left behind routinely.

In subcutaneous mastectomy, a large amount of breast tissue is left beneath the nipple. In subcutaneous and total mastectomy, breast tissue can be left adherent to the skin flaps and on the pectoralis fascia. The amount of residual tissue on the skin flaps is dependent on technique. The thinner the flap made (the less subcutaneous fat left on the flap), the less breast tissue left, but the less viable the flap. A thicker flap (more subcutaneous fat left on the flap) will have a better blood supply and be less subject to ischemia or necrosis but will have more residual breast tissue. In addition, leaving behind the pectoralis fascia makes the surgery easier and decreases blood loss, but breast tissue is left behind on and in the fascia. Although it is tempting to perform lesser surgery in these patients who do not have breast carcinoma, meticulous technique will limit the amount of residual tissue and therefore hopefully decrease the future risk.

If the assumption is made that the efficacy of prophylactic mastectomy is inversely proportional to the amount of breast tissue left behind, then it is obvious that a total mastectomy with thin skin flaps and removal of the pectoralis fascia provides the maximum acceptable surgery for prophylaxis while minimizing residual tissue.

The majority of series in the literature report on subcutaneous mastectomy and therefore their reported rate of the development of new tumors is related to this procedure and not to total mastectomy. In studies in which the site of recurrence is recorded for subcutaneous mastectomy, breast carcinoma developed in the residual tissue below the nipple in 3 of the 11 patients and under the flap in the other 8 patients.[19-26,29] The large amount of tissue left beneath the nipple accounts for the recurrence in that area, whereas recurrence beneath the flap is explained by residual breast tissue left on the flap. Because it technically is more difficult to remove the axillary tail of Spence and harder to make thin flaps during a subcutaneous mastectomy performed through an inframammary crease incision, it is reasonable to assume that subcutaneous mastectomies will lead to a greater incidence of breast carcinoma under the flap than a total mastectomy.

The length of follow-up and the age of the patient are critical factors in determining the number of breast carcinoma cases expected in patients undergoing prophylactic mastectomies, and thus to quantitate the efficacy of the procedure. The number of tumors that would have developed in this population is dependent on the age of the patient (older women are expected to develop more tumors in a given year than younger women) and on the length of time each patient is followed. Only the series by Hartmann et al.[32] takes these 2 factors into account; that author found a 91% reduction in breast carcinoma risk despite the fact that 90% of the mastectomies were subcutaneous. The other series do not provide individual information regarding age, risk, and follow-up and in 1 series, 30% of the patients were lost to follow-up.[27] The case reports[19-25] are unable to provide a denominator, so the percent failing cannot be ascertained.

Factors that might lead to an overestimate of the efficacy of prophylactic mastectomy include inadequate risk assessment and marginal indications for surgery (by today's standards). Today we consider women with lobular carcinoma in situ or a very strong family history suggestive of *BRCA1* or *BRCA2* gene mutations to be at high risk of developing breast carcinoma. Women with atypical hyperplasia are believed to be at moderate risk. In the reports in the literature, the indication for prophylactic mastectomy often was something that one would believe to have little or no impact on risk, such as persistent breast nodules, ductal hyperplasia, papillomatosis, significant macrocystic disease, severe dysplasia on mammogram, or multiple biopsies.[27] Although some prophylactic mastectomies were performed because of a positive family history, the definition of a strong family history was marginal by today's standards. Woods and Meland defined a positive family history as "a maternal history of breast cancer in one or more primary relatives."[28] In the series by Hartmann et al.[32] of 950 patients who underwent bilateral prophylactic mastectomy, 35% did not have a family history, 34% had a family history that was not considered significant by today's standards, and 31% had a strong family history as suggested by multiple relatives, young age at the time of diagnosis, or the presence of ovarian

carcinoma. Judging by this series, <50% of the women undergoing prophylactic mastectomy would have had a significant family history by today's standards and, in the absence of genetic testing, <50% would have been carriers of a gene mutation.

TYPES OF MASTECTOMY

In summary, the literature provides little information that would address the efficacy of prophylactic mastectomy adequately. In this section the techniques of prophylactic mastectomy and reconstruction are discussed.

Subcutaneous Mastectomy

Subcutaneous mastectomy is nearly uniformly followed by submuscular insertion of implants, and the procedure requires approximately 3–5 hours of operative time. In general, the cosmetic result is excellent, but sensation in the nipple usually is diminished or absent. Assuming efficacy is proportional to the amount of breast tissue removed, this procedure is likely to be inadequate. The mammogram shown in Figure 5 gives an idea of how much breast tissue remains after this procedure.

The initial morbidity of the procedure is low and is proportional to the amount of breast tissue removed. The most serious complication is slough or loss of the nipple-areolar complex. This occurs if the nipple-areolar complex is devascularized by removal of the breast tissue below the nipple, and can be prevented by leaving larger amounts of residual breast tissue. This means that the more breast tissue removed, the more effective the procedure will be in preventing breast carcinoma but the greater the risk of loss of the nipple-areolar complex. Conversely, leaving more residual breast tissue will minimize the risk of loss of the nipple-areolar complex but will increase the risk of breast carcinoma in the future.

Long term morbidity is dependent on the method of reconstruction. The use of submuscular implants, which have a limited life expectancy, will necessitate replacement every 5–15 years.[34,35] Because patients undergoing this procedure often are in their 30s, they can expect to undergo 4–8 future surgeries on each side for exchange of implants over a lifetime. Although much concern has been voiced regarding the risk of silicone implants, recent studies do not corroborate the initial concerns. Despite this evidence, the tendency currently is to use saline-filled prostheses, which (although having less theoretic risk) do not have the same consistency or natural feel as silicone and thus result in a less pleasing cosmetic appearance in this situation. Saline implants are adequate for breast augmentation because they are placed beneath normal skin, breast tissue, and muscle, which together hide the texture of the implant. After subcutaneous mastectomy, the implant is only covered by muscle and skin, and its consistency is obvious to the touch.

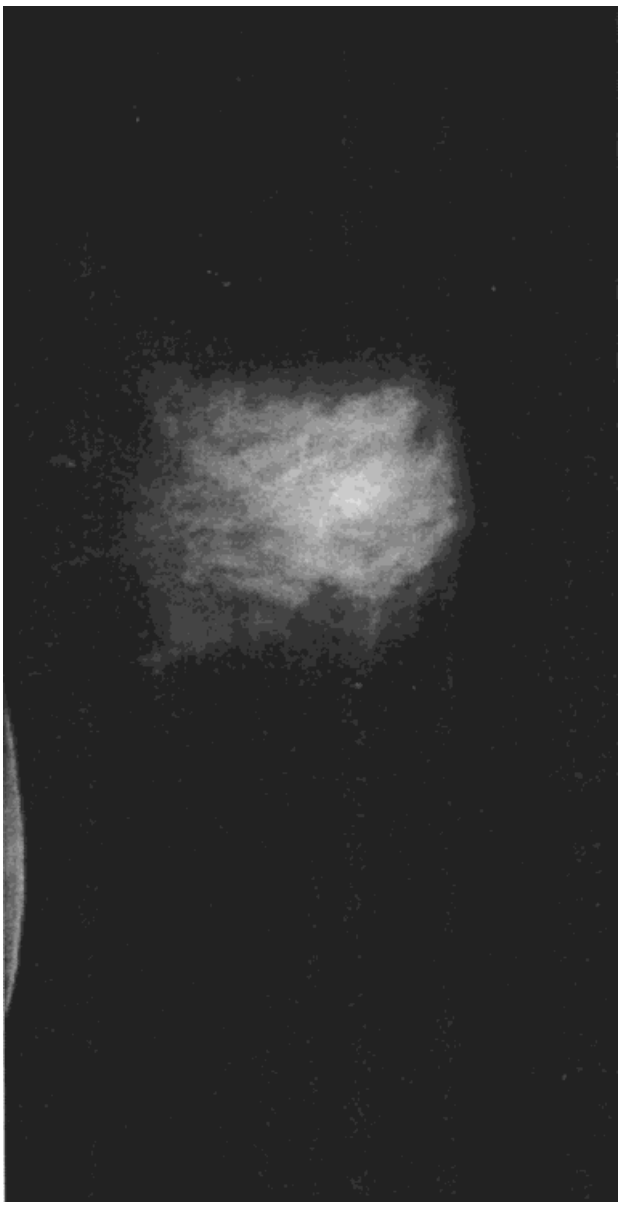

FIGURE 5. This mammogram demonstrates the amount of breast tissue left behind the nipple after a subcutaneous mastectomy.

Due to the large amount of residual breast tissue, these patients require routine mammography and frequent physical examinations at the schedule appropriate to their risk category. The efficacy of screening to detect breast tumors early will be compromised by the presence of an implant. In performing mammography, special distraction views must be undertaken to

assure adequate visualization of all breast tissue. Physical examination may be aided because the implant below the muscle pushes the breast tissue forward where it may be more accessible; however, the soft implant provides a poor base for examination, and a breast mass could be obscured as it is pressed into the soft background.

The false-positive rate (positive findings suggestive of breast carcinoma) for physical examination and mammography most likely will be increased due to the scarring and calcification caused by the initial surgery. This likely will generate additional biopsies in this high risk population. In addition, whereas the average woman can undergo a breast biopsy under local anesthesia with sedation, it will be necessary to use general anesthesia for a woman with an implant to avoid potentially damaging the implant with the needle used to inject local anesthetic.

Due to the large amount of residual breast tissue, the risk of breast carcinoma after subcutaneous mastectomy appears too high to endorse this procedure. Women who already have undergone subcutaneous mastectomy need intensive monitoring with mammography and physical examination, not unlike any woman in her risk category.

Total Mastectomy

Total mastectomy, when performed without reconstruction, requires approximately 2–4 hours of surgical time. In general, the cosmetic result is poor because there is no breast form present and an external prosthesis must be used. Assuming efficacy is inversely proportional to the amount of residual breast tissue, this procedure is likely to be very effective because 90–95% of the breast tissue is removed.

The initial morbidity of the procedure is low but is dependent on the amount of breast tissue removed. The most troubling complication is slough of the skin flap. This occurs if the skin flap is made too thin, causing devascularization. This problem tends to be self-limiting and can be prevented by leaving larger amounts of subcutaneous fat with the flap. This means that the more breast tissue removed, the more effective the procedure will be in preventing breast carcinoma but the greater the risk of skin loss. Conversely, leaving more residual breast tissue will minimize the risk of skin loss but will increase the risk of breast carcinoma in the future. In follow-up, mammography is not necessary.

In the event of the development of breast carcinoma, the efficacy of screening to detect tumors early will be quite good. Physical examination may be aided because the residual breast tissue lies directly against the pectoral muscle, with minimal intervening skin or fat. The chest wall provides a firm surface that makes palpation easy.

The false-positive rate for physical examination will be quite low if the majority of breast tissue has been removed. A suboptimal procedure will leave behind residual breast tissue that may cause incorrect diagnosis of masses in the future and lead to unnecessary biopsies.

BREAST RECONSTRUCTION AFTER TOTAL MASTECTOMY

In the last 20 years, the state of the art in reconstructive surgery has shifted away from implant reconstruction and toward autogenous tissue replacement of the breast mound. These procedures are more complicated and take more surgical time, and their utilization will be dependent on the health of the patient. Because carriers of *BRCA1* and *BRCA2* gene mutations who wish to undergo prophylactic mastectomy are likely to be younger patients in good cardiovascular health, all available options can be used when considering reconstruction. To make an informed choice, patients who are planning to undergo prophylactic mastectomy should be aware of all of the current methods available.

When a patient has chosen to undergo reconstruction, the patient and her surgeon should consider a series of personal choices with respect to: 1) timing of reconstruction (immediate vs. delayed), 2) treatment method (expander/implant, her own tissue, or some combination), and 3) the site of tissue donation if the patient chooses autogenous tissue reconstruction. Preoperative discussion must include a review of the risks and benefits for each method, relative to the patient's age and general health (Figs. 6 and 7).

Regardless of reconstructive method, nipple-areolar reconstruction or tattooing will require a second procedure several months later.

Total Mastectomy with Staged Expander-Implant Reconstruction versus Immediate Implant Reconstruction

Staged Expander-Implant Reconstruction

Expander-implant reconstruction is a staged method of reconstruction utilizing tissue-stretching balloon expanders to recreate the breast mound before placement of a permanent breast prosthesis in a second short procedure. The tissue expander is placed into a submuscular position at the initial mastectomy. In the past, implants were placed into the subcutaneous position, leading to a high complication rate of 25–50%, including exposure, infection, and capsular contracture.[29,36] This subcutaneous technique largely has been abandoned and the current, preferred approach is to place the implant into a submuscular pocket

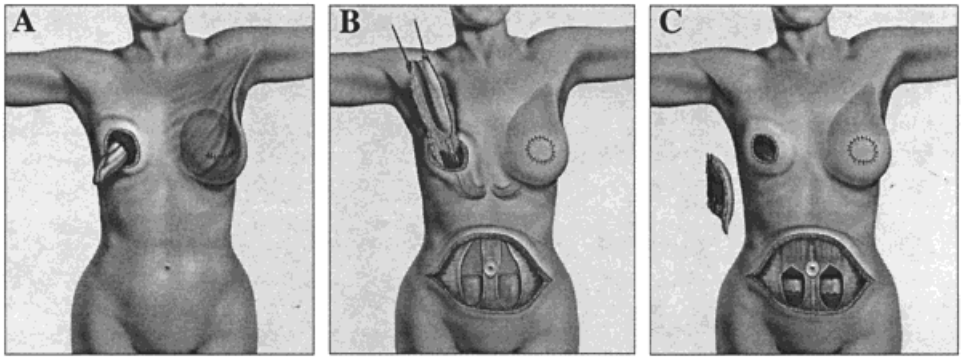

FIGURE 6. The most commonly used reconstruction methods after total mastectomy include (A) submuscular implant, (B) pedicle transverse rectus abdominis myocutaneous (TRAM) flap, and (C) free TRAM flap.

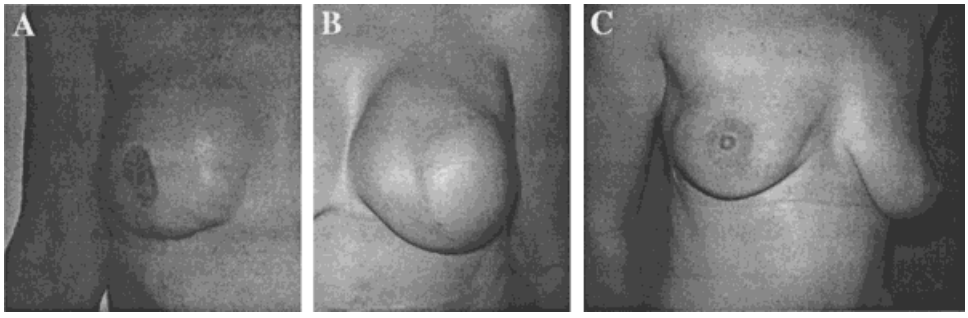

FIGURE 7. Cosmetic results after total mastectomy and reconstruction. (A) Mastectomy and implants, (B) mastectomy and rotation transverse rectus abdominis myocutaneous (TRAM), and (C) mastectomy and free TRAM. All patients underwent delayed reconstruction of the nipple. The arrows shown in the rotation (pedicle) TRAM (panel B) depict a macroscopically visible area of fat necrosis.

behind the pectoralis muscle, utilizing rectus fascia and serratus muscles to cover the inferolateral positions of the implant completely.[37,38] The use of balloon tissue expanders allows the recreation of the preoperative breast size but requires serial outpatient expansions in which saline is instilled into the implant through a buried port. In general, the expander is filled beyond the volume required to restore the preoperative cup size to create enough residual skin to recreate the inframammary fold. Although the initial morbidity of the procedure is low, complications can occur, including infection of the expander, hematoma, skin necrosis, and exposure of the prosthesis, some of which require the expander to be removed completely and another reconstructive approach considered.[29]

Long term morbidity is similar to that of patients who undergo immediate final placement of a prosthesis or cosmetic augmentation, and it is related primarily to the implant. Complications include wrinkling, scarring, and capsular contracture, which can lead to a hard mound, a poor aesthetic appearance, or rupture of the implant. The implants are likely to require replacement every 5–15 years.[34,35] In a young patient in her 30s with bilateral prophylactic mastectomies and implant reconstruction, the normal life expectancy of the prosthesis may result in the need for 4-8 replacement procedures for each breast during her lifetime. The need for serial implant replacement must be discussed as one of the factors influencing the choice of reconstructive method before prophylactic mastectomy is performed.

Immediate Implant Reconstruction

On occasion, implant reconstruction can be performed in a single step, by placing the appropriate implant initially at the time of mastectomy. In general, this procedure is reserved for patients with smaller breasts without significant ptosis. It is difficult to avoid postoperative skin slough if the native breast skin flaps are closed with tension over a large implant.

Immediate placement of the permanent prosthesis requires accepting a smaller breast size because the nipple-areolar complex and some adjoining skin will have been removed, decreasing the size of the breast mound. Immediate submuscular implants can provide reasonable results if bilateral reconstruction is required because both breasts then can be reduced in size symmetrically. In general, this reconstructive method adds only 1–2 hours to surgical time when performed immediately after mastectomy.

Long term follow-up after implant reconstruction is straightforward; it should be easy to palpate the rare areas of residual breast tissue within the skin flaps or pectoralis fascia over the submuscular implant by self-examination or by clinical examination, but a soft implant may obscure palpable masses. Palpable masses may require biopsy, which should be performed under general anesthesia to avoid puncturing

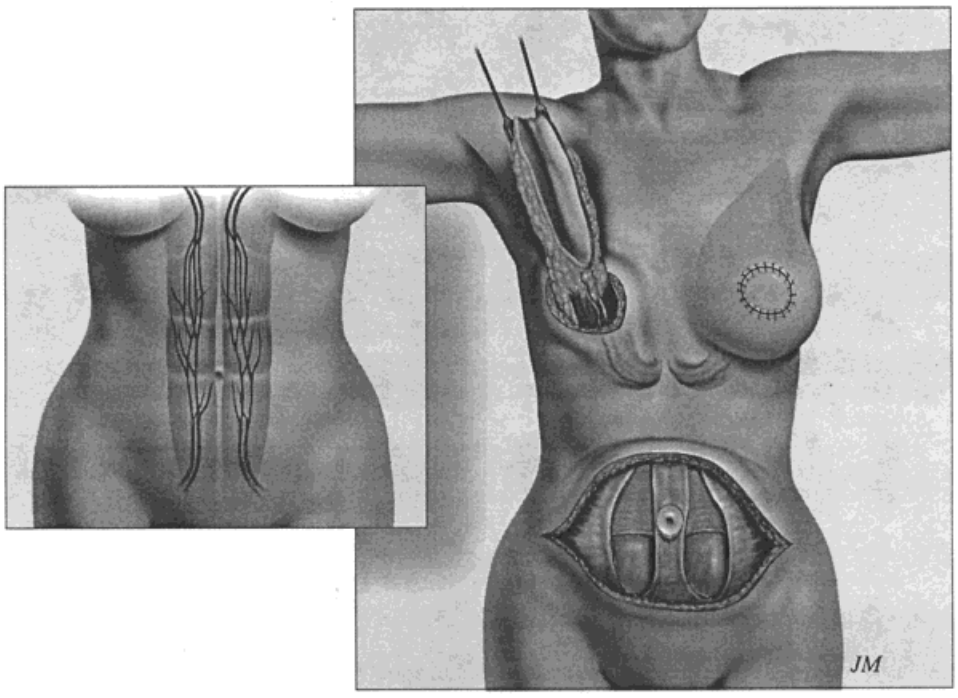

FIGURE 8. Pedicle transverse rectus abdominis myocutaneous flap reconstruction of the breast uses the skin and subcutaneous fat of the lower abdomen to replace the breast mound. The skin and fat are rotated to the breast defect based on the vascular pedicle of the superior epigastric artery contained within the rectus abdominis muscle. The inferior epigastric artery is transected and ligated.

the implant with a needle. Mammography of the reconstructed breast is not necessary.

Autogenous Tissue Reconstruction

Advances in surgical technique and a dissatisfaction with the complications and results of implant reconstruction have led to the increasing popularity of autogenous tissue methods of reconstruction.[39] This is particularly true among younger patients who do not wish to face repeated surgeries for the management of ruptured implants through their lifetime. Autogenous tissue reconstruction provides the ability to create a more mature, ptotic breast mound and the ability to restore lost skin to the mastectomy wound while eliminating the implant-associated problems of capsular contracture and rupture.

All methods of tissue reconstruction add significantly to the duration of surgery, a risk that must be weighed against the patient's physiologic status. If a patient chooses her own tissue for reconstruction, a variety of reconstructive methods, including rotation or pedicle flaps and microsurgical transplantation, are available. These procedures can harvest tissue from an arsenal of donor sites, including the abdomen, back, buttock, and thigh.[40] Choice of procedure and site of tissue donation will be discussed at this time.

Pedicle Transverse Rectus Abdominis Myocutaneous Flap Reconstruction

Pedicle transverse rectus abdominis myocutaneous (TRAM) flap breast reconstruction currently is the most popular method of autogenous tissue reconstruction, and was introduced by Hartrampf et al. in 1982.[41] The flap uses the skin and subcutaneous fat of the lower abdomen, rotated to the breast defect based on the vascular pedicle of the superior epigastric artery contained within the rectus abdominis muscle (Fig. 8).[42] The breast mound is reconstructed after mastectomy within the native breast skin envelope, replacing resected skin as needed. Although the procedure sounds extensive, the harvesting of the donor fat and skin is the same procedure used in a cosmetic abdominoplasty ("tummy tuck"). Therefore the procedure also improves abdominal contour and firmness, a benefit universally popular among patients.[39] In this procedure, the rectus abdominis muscle is transected at or near the pubis, capturing the periumbilical perforators to the skin coming through the rectus muscle. The abdominal tissue then is tunneled to the mastectomy wound to provide tissue for the breast mound.

Compared with implant reconstructions, the extent of surgery prolongs both hospitalization (4–7 days) and perioperative recovery (4–6 weeks). Flap-associated complications, particularly partial flap loss and fat necrosis, can affect up to 30% of pedicle TRAM patients and are increased by preoperative obesity and smoking.[43,44] These complications often lead to additional procedures to remove fat necrosis or scar tissue, both for cosmetic result and to rule out the possibility that these areas represent malignancy. These secondary revision procedures usually are per-

formed in an outpatient setting and occasionally can be combined with nipple-areolar reconstruction.

In the TRAM procedure for bilateral reconstruction, restoration of the breast mound is limited by the availability of abdominal pannus or fat, which must be split in the midline to provide symmetry. Therefore, the final breast size may be smaller than the preoperative size.

Long term follow-up of patients who have undergone TRAM flap reconstruction requires serial examinations by experienced observers. Mammography of the TRAM flap is not necessary and even may be confusing because fat necrosis causes scarring and calcifications that may be mistaken for tumor and lead to unnecessary biopsies. As more experience is gained, mammography of the reconstructed breast may help to reduce anxiety if typical features of fat necrosis are observed.[45] The presence of the flap does not permit easy examination of the pectoral fascia, which should be removed with the mastectomy specimen. This procedure has been proven to be oncologically safe in the treatment of breast carcinoma patients and does not obscure recurrence of disease.[46,47]

Microsurgical TRAM Flap Reconstruction

In pedicle TRAM reconstruction, as described previously, the volume of the breast that can be reconstructed is limited by several factors, including the blood supply, the patient's body habitus, and the presence of previous abdominal surgical scars. The blood supply is of particular significance because the procedure depends on the adequacy of the secondary circulation to the rectus muscle through the superior epigastric artery. Reconstructive surgeons have attempted to improve flap circulation by either "supercharging" the TRAM flap by augmenting the superior epigastric blood flow with microsurgical anastomoses of the primary blood supply through the deep inferior epigastric system to axillary vessels[48] or by complete microsurgical transplantation of the abdominal tissue based on the deep inferior (dominant) epigastric pedicle, the so-called "free" TRAM.[49] Microsurgical free TRAM flap reconstruction has several advantages over conventional pedicle techniques, despite the increased duration and complexity of the procedure. The extent of abdominal surgery is less, the need for full muscle harvest and tunneling is abrogated, the amount of muscle harvested can be greatly reduced, and restoration of the primary blood supply of the flap through the deep inferior epigastric artery has been found to result in a reduction in fat necrosis.[50,51] Although not without risks,[50] the frequency of flap loss, partial skin loss, fat necrosis, and abdominal herniation can be reduced to between 1–5%, well below that observed in conventional pedicle TRAM flaps.[44,51,52]

Microsurgical breast reconstruction adds additional surgical time to the mastectomy (6–12 hours) and carries with it the risk of vessel thrombosis leading to complete loss of the reconstruction. Despite this risk, flap loss is uncommon[43,51] and cosmetic results are excellent. The free mobility of the flap allows superior shaping and the inframammary fold remains intact because tunneling is unnecessary. Follow-up requires a similar approach to pedicle TRAM, with serial physical examination. Because of the appreciable decrease in fat necrosis, the rate of false-positive findings on physical examination and the rate of secondary biopsies should be decreased considerably.

Other Reconstructive Approaches

For patients who lack sufficient abdominal tissue to provide for pedicle or microsurgical TRAM flap reconstruction, other donor sites for free tissue transplantation to the breast mound have been utilized, including thigh, buttock, and pelvic rim.[40]

Latissimus Flap Reconstruction

In selected patients, the latissimus flap can be used for reconstruction of the breast. If adequate tissue is available for a smaller breast mound, the latissimus flap may suffice for reconstruction. However, the combined use of latissimus flap and implant reconstruction often is required to restore adequate volume to the breast mound.[35] This method harvests the latissimus muscle and the overlying soft tissue from the back based on the thoracodorsal artery and vein, which is transposed anteriorly to recreate the breast mound. Bilateral reconstruction, although possible, is more difficult due to the required repositioning of the patient intraoperatively from one side to the other to permit exposure of the back, axilla, and breast. Unilateral reconstruction can be quite effective, allowing patients who do not wish to undergo serial expansion and subsequent second-stage placement of an implant to complete their reconstruction in one stage. Unfortunately, although quite reliable, this method of reconstruction combines the risks of a flap procedure (longer surgery, donor site harvest, and hematoma) with those related to implants, such as capsular contracture and rupture of the implant.

Long term follow-up is similar to that of TRAM reconstruction, primarily through serial physical examination. With the use of an implant, the implant remains deep to the muscle layer, permitting detection of developing tumors over the implant by palpation.

TABLE 2
Types of Reconstruction

	Total mastectomy and implants	Total mastectomy and rotation TRAM	Total mastectomy and free TRAM
Surgery	4–6 hours	6–8 hours	6–12 hours
Cosmetic result	Good	Very good	Excellent
Efficacy	Removes 90–95% of tissue	Removes 90–95% of tissue	Removes 90–95% of tissue
Follow-up	Physical examination	Physical examination	Physical examination
False-negative rate	Low	High	Moderate
False-positive rate	Low	Highest	Moderate
Morbidity			
Short term	Moderate	High	Very high
Long term	High	Moderate	Small

TRAM: transverse rectus abdominis myocutaneous.

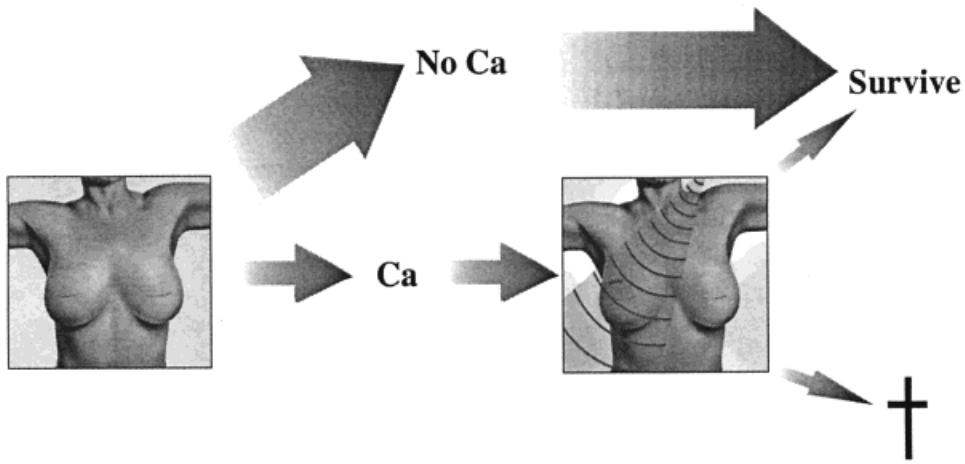

FIGURE 9. Possible outcomes of prophylactic mastectomy. If all women carrying mutations in the *BRCA1* and *BRCA2* genes undergo prophylactic mastectomy, theoretically a large number will not develop breast carcinoma (ca) and therefore will not die of breast carcinoma. However, an undetermined number of women will develop breast carcinoma in the flap, will be treated by excision plus radiation, and will either be cured or die. The size of the arrows is a visual representation of the number of patients expected to move down each pathway. The exact size of the arrows will be determined by future research.

SUMMARY OF RECONSTRUCTION OPTIONS

Women carrying gene mutations in *BRCA1* and *BRCA2* who undergo prophylactic mastectomy should undergo reconstruction at the same time as that procedure. Immediate reconstruction allows conservation of the maximum amount of native breast skin, and therefore provides a vastly superior cosmetic result when compared with delayed reconstruction. The attributes of the major types of reconstruction are summarized in Table 2. Although reconstruction theoretically will mask the occurrence of new breast tumors arising in residual breast tissue, this risk is most likely small, and the psychosocial benefits of reconstruction are great. In terms of reconstruction, our preference is for autogenous tissue, ideally the free TRAM procedure.

OUTCOMES OF PROPHYLACTIC MASTECTOMY

The efficacy of prophylactic mastectomy in women who carry a *BRCA1* or *BRCA2* gene mutation has not been tested. Women with mutations need to be followed intensively, regardless of whether they choose prophylactic mastectomy or intensive surveillance, and the rate of development of breast carcinoma, the morbidity of treatment, and the rate of death must be monitored. Although instances of new, primary breast carcinoma after prophylactic mastectomy do exist, overall the rate of breast carcinoma does appear to be decreased by this procedure. Although it is not possible to remove all breast tissue, the literature and expert opinion suggest that removal of 90–95% of breast tissue removes 90–95% of the risk. Whether the results in patients at low risk can be extrapolated to *BRCA1* and *BRCA2* gene mutation carriers needs to be examined.

The possible outcomes of prophylactic mastectomy are depicted in Figure 9. If all women carrying gene mutations in *BRCA1* and *BRCA2* undergo prophylactic mastectomy, theoretically a large number will not develop breast carcinoma and therefore will

not die of breast carcinoma. However, some undetermined number of women will develop breast carcinoma under the flap, will be treated by excision plus radiation, and either will be cured or die. The size of the arrows in Figure 9 are roughly proportional to the number of women predicted to progress along each path and will change as our understanding of the natural history and treatment of these patients increases.

GENETIC TESTING AND PROPHYLACTIC SURGERY

It is our opinion that a woman who is considering prophylactic surgery should be encouraged to undergo genetic testing for hereditary susceptibility to breast carcinoma. If the testing conclusively shows she does not carry a deleterious mutation, an attempt should be made to dissuade her from her decision. She most likely is at no more risk than the general population, and prophylactic surgery is not indicated at that risk level. If the testing conclusively shows she does carry a deleterious mutation, then prophylactic surgery should be considered and discussed in the context of the information presented in the current study. If the testing is inconclusive, the risk estimate based on pedigree analysis combined with the likelihood of a false-negative test should be used to determine the appropriate course of action.

CONCLUSIONS

Women with a *BRCA1* or *BRCA2* gene mutation must choose between prophylactic mastectomy or intensive surveillance (with or without chemoprevention). In making this choice, the advantages and limitations of each approach must be compared objectively. Currently, we believe that the relative efficacy of screening and the impending improvements in screening, chemoprevention, and treatment make intensive screening a close alternative to prophylactic mastectomy. When advising a woman who carries a *BRCA1* or *BRCA2* gene mutation, we discuss the pros and cons of screening, chemoprevention, and prophylactic surgery. In the future, we can look forward to considerable improvements in screening, chemoprevention, and treatment, making prophylactic mastectomy obsolete. Until then, it remains a useful part of our armamentarium.

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