

# The New England Journal of Medicine

© Copyright, 1999, by the Massachusetts Medical Society

VOLUME 340

JANUARY 14, 1999

NUMBER 2



## EFFICACY OF BILATERAL PROPHYLACTIC MASTECTOMY IN WOMEN WITH A FAMILY HISTORY OF BREAST CANCER

LYNN C. HARTMANN, M.D., DANIEL J. SCHAID, PH.D., JOHN E. WOODS, M.D., THOMAS P. CROTTY, M.D.,  
JEFFREY L. MYERS, M.D., P.G. ARNOLD, M.D., PAUL M. PETTY, M.D., THOMAS A. SELLERS, PH.D.,  
JOANNE L. JOHNSON, R.N., SHANNON K. McDONNELL, M.S., MARLENE H. FROST, PH.D., R.N.,  
AND ROBERT B. JENKINS, M.D., PH.D.

### ABSTRACT

**Background** Options for women at high risk for breast cancer include surveillance, chemoprevention, and prophylactic mastectomy. The data on the outcomes for surveillance and prophylactic mastectomy are incomplete.

**Methods** We conducted a retrospective study of all women with a family history of breast cancer who underwent bilateral prophylactic mastectomy at the Mayo Clinic between 1960 and 1993. The women were divided into two groups — high risk and moderate risk — on the basis of family history. A control study of the sisters of the high-risk probands and the Gail model were used to predict the number of breast cancers expected in these two groups in the absence of prophylactic mastectomy.

**Results** We identified 639 women with a family history of breast cancer who had undergone bilateral prophylactic mastectomy: 214 at high risk and 425 at moderate risk. The median length of follow-up was 14 years. The median age at prophylactic mastectomy was 42 years. According to the Gail model, 37.4 breast cancers were expected in the moderate-risk group; 4 breast cancers occurred (reduction in risk, 89.5 percent;  $P < 0.001$ ). We compared the numbers of breast cancers among the 214 high-risk probands with the numbers among their 403 sisters who had not undergone prophylactic mastectomy. Of these sisters, 38.7 percent (156) had been given a diagnosis of breast cancer (115 cases were diagnosed before the respective proband's prophylactic mastectomy, 38 were diagnosed afterward, and the time of the diagnosis was unknown in 3 cases). By contrast, breast cancer was diagnosed in 1.4 percent (3 of 214) of the probands. Thus, prophylactic mastectomy was associated with a reduction in the incidence of breast cancer of at least 90 percent.

**Conclusions** In women with a high risk of breast cancer on the basis of family history, prophylactic mastectomy can significantly reduce the incidence of breast cancer. (N Engl J Med 1999;340:77-84.)

©1999, Massachusetts Medical Society.

THE availability of improved means to identify women at high risk for breast cancer, such as genetic testing for *BRCA1* and *BRCA2* mutations, intensifies the need to define the benefits and risks of early detection and protective measures for such women.

Prophylactic mastectomy, either total or subcutaneous mastectomy, is one option for the prevention of breast cancer.<sup>1</sup> Specific indications for prophylactic mastectomy include a family or personal history of breast cancer, multiple previous breast biopsies, unreliable results on physical examination because of nodular breasts, findings of dense breast tissue on mammography, mastodynia, and cancerphobia.<sup>2,3</sup> Although prophylactic mastectomy has been used for decades, there is little information regarding the long-term effectiveness of this procedure.<sup>4-6</sup> Surgeons have long recognized that breast tissue is widely distributed over the entire anterolateral portion of the chest wall and axilla and that no mastectomy removes all mammary tissue.<sup>7</sup> There have been case reports of breast cancer in residual glandular epithelium after either total or subcutaneous prophylactic mastectomy.<sup>8-10</sup>

One study of prophylactic mastectomy included 1500 women who underwent subcutaneous mastectomy.<sup>11,12</sup> Patients were identified by soliciting information from members of the American Board of Plastic Surgery; 165 plastic surgeons contributed data.

From the Divisions of Medical Oncology (L.C.H., M.H.F.), Biostatistics (D.J.S., S.K.M.), Plastic and Reconstructive Surgery (J.E.W., P.G.A., P.M.P.), and Clinical Epidemiology (T.A.S., J.L.J.), and the Department of Laboratory Medicine and Pathology (J.L.M., R.B.J.), Mayo Clinic and Mayo Foundation, Rochester, Minn.; and the Department of Pathology, St. Vincent's Hospital, Dublin, Ireland (T.P.C.). Address reprint requests to Dr. Hartmann at the Department of Oncology, Mayo Clinic, 200 First St. S.W., Rochester, MN 55905.

Other authors were Clive S. Grant, M.D., of the Department of Surgery, and Virginia V. Michels, M.D., of the Department of Medical Genetics, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Twenty percent of the patients had a first-degree relative with breast cancer. Breast cancer developed in six women after the procedure, and the authors concluded that subcutaneous mastectomy was an effective means of prophylaxis.<sup>12</sup> Issues of concern with respect to this study include the possibility of selection bias toward the inclusion of patients with a favorable outcome, a rate of loss to follow-up of 30 percent, the inclusion of women with cancer in the surgically treated breast, the lack of definition of the underlying risks of breast cancer, and the lack of a central review of the pathological specimens.

To provide guidance regarding prophylactic mastectomy for high-risk women and their care givers, models have been designed to estimate the gain in life expectancy with prophylactic mastectomy (as compared with no prophylactic mastectomy) among carriers of *BRCA1* or *BRCA2* mutations.<sup>13,14</sup> Such approaches are highly dependent on assumptions regarding the efficacy of the procedure. In their model, Schrag et al. used an estimate of an 85 percent reduction in risk with prophylactic mastectomy<sup>13</sup>; Grann et al. assumed a 90 percent reduction in risk with the procedure.<sup>14</sup> For women who are contemplating this intervention, it is imperative to have reliable data on the outcomes of prophylactic mastectomy in a well-defined cohort.

We conducted a retrospective analysis of all women with a family history of breast cancer who underwent prophylactic mastectomy at the Mayo Clinic between 1960 and 1993. We sought to define the effect of the procedure on the subsequent incidence of breast cancer and on the risk of death from the disease. We analyzed the clinical characteristics of women who underwent bilateral prophylactic mastectomy, their underlying risk of breast cancer, and the subsequent occurrences of breast cancer in these women. To predict the number of breast cancers expected in the absence of prophylactic mastectomy, we used the model of Gail et al.<sup>15</sup> for women at moderate risk because of a familial history of cancer and a control group of the sisters of the study subjects for women at high risk.

## METHODS

### Identification of the Study Subjects

Because there is no standardized or institutional code for prophylactic mastectomy, we obtained the charts from the surgical index recording system of the Mayo Clinic of all women who had undergone bilateral subcutaneous mastectomy or bilateral total mastectomy between January 1, 1960, and December 31, 1993. The starting date of 1960 was chosen because the availability of breast implants in the 1960s allowed reconstruction after prophylactic mastectomy, making the procedure more acceptable and more common. Either bilateral subcutaneous mastectomy or total mastectomy was performed on 1065 women during the period of study. All charts were reviewed by one of two trained nurses to determine indications for the procedure, risk factors for breast cancer, complications of surgery, and occurrences of cancer. A study-specific questionnaire was sent to all women or, if they were

deceased, to their next of kin. Twenty-five women were excluded for the following reasons: breast cancer in the surgically treated breast (six women), augmentation or reduction only (nine), male sex (four), incorrect surgical code (five), and no authorization for inclusion in research (one). A total of 639 had a family history of breast cancer. An additional 401 women with no family history of breast cancer had undergone either bilateral subcutaneous mastectomy or total mastectomy for a variety of breast problems including nodular breasts, multiple prior breast biopsies, and refractory mastodynia.

### Definition of High Risk and Moderate Risk

We categorized women with a family history of breast cancer into moderate-risk and high-risk groups. A family at high risk has features suggestive of an autosomal dominant predisposition to breast cancer. Established criteria for high-risk status include the following: one or more relatives with breast cancer, early age at the diagnosis of cancer, and a family history of ovarian cancer, bilateral breast cancer, or breast cancer in male members.<sup>6,16-18</sup> The criteria we used are listed in Table 1; 214 women met the criteria. Women who did not meet these criteria were considered to be at moderate risk. Of the 425 women in the moderate-risk category, 268 had at least one affected first-degree relative, 46 had two aunts, cousins, or both with breast cancer, and 111 had family histories of breast cancer involving fewer second-degree or third-degree relatives.

### Data Collection and Follow-up

The study-specific questionnaire requested information on the following: risk factors for breast cancer (including a family history of breast cancer), occurrences of cancer in the proband, occurrence of surgical complications of prophylactic mastectomy, reasons for prophylactic mastectomy, and the psychosocial effect of the procedure. Women whose charts or questionnaires indicated that they were members of high-risk families were telephoned to confirm the family history and to obtain information on histories of cancer in any sisters. The patients were also telephoned as needed to complete follow-up information.

### Review of Pathological Specimens

All available specimens obtained at prophylactic mastectomy and in subsequent cases of breast cancer were reviewed by one of the two participating pathologists. The specimens obtained at prophylactic mastectomy were categorized as follows: normal, with nonproliferative changes; proliferative changes without atypia; atypical hyperplasia; carcinoma in situ; or invasive carcinoma. The specimens obtained in cases of breast cancer after prophylactic mastectomy were reviewed to confirm the presence of cancer.

### Surgical Techniques

The technique of subcutaneous mastectomy has been described in detail elsewhere.<sup>19,20</sup> The majority of breast tissue ( $\geq 90$  percent) is removed, leaving residual tissue immediately beneath the nipple and areola, where it is readily palpable.

The technique of total mastectomy has been described in detail elsewhere.<sup>21</sup> In brief, the entire breast is removed, including the nipple-areolar complex. The axillary nodes are not dissected. The pectoralis muscles are preserved.

### Statistical Analysis

#### Gail Model

The Gail model offers a way to predict what would have been the expected incidence of breast cancer in the cohort of women who elected to undergo bilateral prophylactic mastectomy. This model was based on data for 243,221 white women who were screened for breast cancer annually for five years.<sup>15</sup> Women with breast cancer at the first screening were removed from the analysis. Our patient population was similar to the one in the model, being

**TABLE 1. CRITERIA FOR ENROLLMENT IN THE HIGH-RISK CATEGORY.\***

Two or more first-degree relatives with breast cancer
One first-degree relative and two or more second-degree or third-degree relatives with breast cancer
One first-degree relative with breast cancer before the age of 45 years and one other relative with breast cancer
One first-degree relative with breast cancer and one or more relatives with ovarian cancer
Two second-degree or third-degree relatives with breast cancer and one or more with ovarian cancer
One second-degree or third-degree relative with breast cancer and two or more with ovarian cancer
Three or more second-degree or third-degree relatives with breast cancer
One first-degree relative with bilateral breast cancer

\*To be considered at high risk, women had to meet at least one of these criteria.

free of cancer on clinical or imaging studies before prophylactic mastectomy. The risk factors considered in the calculation of the expected number of breast cancers with the Gail model include the age at menarche, the age at first live birth, the number of previous breast biopsies, whether atypical hyperplasia is present, and the number of first-degree female relatives (specifically, mother and sisters) with breast cancer.

The interval included in the prediction of the occurrence of breast cancer began at the time of prophylactic surgery and ended at the time of the diagnosis of breast cancer, the last follow-up visit, or death. The Gail model can be used to predict a woman's risk only until the age of 80. For women who were followed beyond the age of 80, the average annual risk from the ages of 75 through 80 was used to extrapolate the risk to the age at the last follow-up visit.

#### Control Study of Sisters of the High-Risk Probands

The Gail model was not developed for use in women with strong family histories. To estimate the number of breast cancers that would have been expected in our high-risk group, we performed a control study of sisters of the high-risk probands. The following data were collected for all biologic sisters of the high-risk probands: year of birth; history of breast cancer and date of diagnosis; time of prophylactic mastectomy, if performed, and year of procedure; vital status; and year and cause of death.

To calculate the number of breast cancers expected among the high-risk probands in the absence of prophylactic mastectomy, we used the age-specific rates of breast cancer among their sisters. These rates were then applied to the probands, beginning at the time of surgery and ending at the end of follow-up (defined as the occurrence of breast cancer, death, or the end of follow-up). Sisters who had undergone bilateral prophylactic mastectomy were excluded. The rate among the sisters was calculated in three ways. First, we counted all breast cancers that occurred during all the years of follow-up, accounting for age-specific person-years of observation, beginning at the age of 18 years. Because women may elect to undergo prophylactic mastectomy because of a history of breast cancer in the family, this approach could lead to oversampling of data from sisters with breast cancer and subsequent overestimates of the number of expected breast cancers. Thus, we calculated the rate in a second way by including only data on sisters whose breast cancer occurred after their respective proband's prophylactic mastectomy. However, some probands were classified as having families with a high risk of cancer either partially or wholly as a result of the occurrence of breast cancer among sisters. The use of a subgroup ascertained in this way can

also artificially inflate the rate of breast cancer among the entire group of sisters. Hence, we calculated the rate in a third way using Weinberg's method for correcting for multiple ascertainment.<sup>22,23</sup> This method has been widely used in classic segregation analyses in cases in which the objective is to obtain an estimate of the incidence of disease within families, after adjustment for the inclusion of a family simply because it has multiple members with the disease. For this analysis, all breast cancers among the sisters (before and after the respective proband's prophylactic mastectomy) were included.

#### Death from Breast Cancer

In the moderate-risk group, we used the Gail model's prediction of the incidence of breast cancer as the basis for a calculation of the risk of death from breast cancer. First, we calculated the probability of breast cancer for each year of follow-up using the Gail model. We then multiplied the values by the probability of death from invasive breast cancer for each year during the remaining follow-up period (the interval from the predicted occurrence of breast cancer to the end of follow-up) and totaled these results to determine the risk during the entire period of follow-up.

Since the Gail model predicts the numbers of both invasive and in situ breast cancers expected annually, these values were multiplied by 0.9, because we assumed that 90 percent of the breast cancers that occurred during the period of study would be invasive.<sup>24</sup> We assumed that there would be no increase in mortality associated with in situ disease.<sup>25</sup> We estimated the probability of death from invasive cancer during the remaining follow-up period by applying breast-cancer relative-survival rates from the Surveillance, Epidemiology, and End Results data<sup>26</sup> to age-specific survival rates among white women in the United States.<sup>27-29</sup> The reduction in risk was calculated with use of the following equation:  $100 (1 - \frac{\text{number of observed events}}{\text{number of expected events}})$ , with 95 percent confidence intervals computed by the Poisson distribution for the number of observed events. In the high-risk group, we calculated the expected number of deaths from breast cancer, using the rates among the sisters of the probands, using the same methods that we used to determine the incidence rates among the sisters.

## RESULTS

### Characteristics of the Patients

A total of 639 women with a family history of breast cancer underwent bilateral prophylactic mastectomy between 1960 and 1993. Of these, 425 had a moderate risk of breast cancer on the basis of family history, and 214 had a high risk, having met at least one of the criteria listed in Table 1. The 214 high-risk women were from 203 families (Table 2). Other characteristics of the women are listed in Table 3. Ninety-four percent of the women elected to undergo breast reconstruction after prophylactic mastectomy.

### Vital Status and Follow-up

Of the 639 women, 609 (95 percent) were alive at the time of the analysis and 30 (5 percent) were dead. Complete questionnaire and chart information was available for 593 women. We were unable to locate 14 women (2 percent), and 32 women or next of kin (5 percent) declined to fill out the questionnaire. Nevertheless, we had medical-record information for all women, including data on the occurrence of cancer and on some risk factors. The median length of follow-up was 14 years (9095 person-years),

**TABLE 2.** CHARACTERISTICS OF 203 HIGH-RISK FAMILIES.\*

NO. OF BREAST CANCERS IN FAMILY	NO. OF FAMILIES	NO. OF AFFECTED FIRST-DEGREE RELATIVES					EARLIEST AGE AT DIAGNOSIS OF BREAST CANCER				HISTORY OF OVARIAN CANCER IN FAMILY		
		0	1	2	3	4	<45 YR	45-60 YR	>60 YR	UNKNOWN	YES	NO	
		number of families											
1	7	1	6				3		3	1		6	1
2	46	3	21	22			31	11	3	1		11	35
3	62	8	31	18	5		36	19	4	3		16	46
4	44	7	20	11	6		23	18	2	1		6	38
5	16	2	3	2	8	1	13	3				4	12
6	13	3	5	3	2		11	1	1			6	7
7	8		3	3	2		7	1				5	3
8	4		3	1			2	1	1			1	3
9	1			1			1						1
10	1			1			1					1	
14	1		1				1						1

\*There were 214 probands from these 203 families.

**TABLE 3.** CHARACTERISTICS OF THE 639 MODERATE-RISK AND HIGH-RISK WOMEN WHO UNDERWENT BILATERAL PROPHYLACTIC MASTECTOMY.

CHARACTERISTIC	MODERATE RISK (N=425)	HIGH RISK (N=214)
Age at mastectomy (yr)		
Median	42	42
Range	18-79	20-75
Age at menarche (yr)		
Median	13	13
Range	7-17	9-17
Nulliparous (%)	12	13
Age at first live birth (yr)		
Median	21	21
Range	15-43	15-41
Mean no. of breast biopsies before mastectomy	2.4	1.9
Type of mastectomy (%)		
Subcutaneous	90	89
Total	10	11

with a minimum of 2 years of follow-up for 99 percent of the cohort.

**Incidental Breast Cancer**

Among the women who were assessed for the study, six were found to have an incidental breast cancer at the time of prophylactic mastectomy. They were treated for breast cancer and therefore were not included in the cohort of 639 women who were at risk for the disease. These incidental cancers were not considered failures of prophylaxis. At the end of the

follow-up period, all six women were alive and free of disease (median follow-up, 8 years; mean, 10.2).

**Review of Pathological Specimens**

Tissue obtained during prophylactic mastectomy in 603 women was available for review (tissue from both breasts was available for 583 women, and tissue from only one breast was available for 20). No tissue was available for 36 women; the majority underwent mastectomy in the 1960s. The pathologists categorized the specimens as normal, with no proliferative changes, in 74.5 percent of cases; as having proliferative changes without atypia in 23.9 percent of cases; as having atypical hyperplasia in 1.5 percent of cases; and as invasive carcinoma in 0.1 percent. None of the specimens were categorized as carcinoma in situ. Two invasive cancers that were identified during the pathological review were not so identified at the time of mastectomy. Breast cancer developed in one of these two women three years after prophylactic mastectomy. The other woman had no evidence of breast cancer 19 years after prophylactic mastectomy.

**Breast Cancer after Prophylactic Mastectomy**

Breast cancers developed in seven women after prophylactic mastectomy (Table 4). Six cancers were confined to the chest wall at diagnosis. One woman in the high-risk group presented with bone metastases from an adenocarcinoma 12 years after prophylactic mastectomy; immunostaining was negative for estrogen receptors and progesterone receptors, but positive for cystic disease fluid protein 15 (a mammary-tumor marker). Examination of the chest wall and mammography of residual breast tissue were negative.

The median time from mastectomy to the devel-

**TABLE 4.** CHARACTERISTICS OF SEVEN WOMEN WITH BREAST CANCER AFTER BILATERAL PROPHYLACTIC SUBCUTANEOUS MASTECTOMY.

PATIENT No.	LOCATION	YEARS AFTER MASTECTOMY	FAMILY HISTORY
1	Left breast	15	Moderate risk
2	Chest wall	2	Moderate risk
3	Left breast, "above areola"	5	Moderate risk
4	Chest wall	25	Moderate risk
5	Bone marrow	12	High risk
6	Left lateral side of chest wall	3	High risk
7	Left nipple	6	High risk

oment of breast cancer was 6 years (range, 2 to 25). All seven women had undergone bilateral subcutaneous mastectomy. There was no significant difference in the incidence of breast cancer between the women who underwent subcutaneous mastectomy and those who underwent total mastectomy (7 of 575 women vs. 0 of 64 women,  $P=0.38$ ); however, with so few events, the statistical power is weak.

Two of the seven women died of breast cancer; they survived a mean of 1.5 years after the diagnosis. At the end of follow-up, five were alive a median of 8 years (mean, 10) after diagnosis and were free of disease after local treatment of their chest-wall disease. Tissue from four of these women was available for review. In the case of two women, we relied on letters from their physician reporting breast cancer.

In the case of the seventh patient, she reported having cancer, but no additional documentation was available.

#### Incidence of Breast Cancer

##### Moderate-Risk Group

According to the Gail model, the predicted incidence of breast cancer among the 425 moderate-risk women, with a median follow-up of 14 years, was 37.4. The actual incidence was 4 (Table 4). Thus, the reduction in the risk of breast cancer was 89.5 percent ( $P<0.001$ ) after prophylactic mastectomy in women with a moderate risk of breast cancer on the basis of family history.

##### High-Risk Group

The 214 high-risk women had a total of 403 sisters. When the data from the age of 18 to the end of follow-up were analyzed, 156 of the sisters (38.7 percent) were found to have had breast cancer (115 cancers were diagnosed before the respective proband's prophylactic mastectomy and 38 afterward; the time of the diagnosis was unknown in 3 cases). The incidence of breast cancer among the sisters was calculated in three ways: in the first, all breast cancers from the age of 18 to the end of follow-up were included; in the second, the number of breast cancers from the age of 18 to the end of follow-up was corrected for ascertainment bias; and in the third, only breast cancers that occurred after the respective proband's prophylactic mastectomy were included. We then calculated the expected number of breast cancers among the probands (Table 5). With the use of the first method, the expected number was 52.9. After correction for ascertainment bias, the number was 30.0. With the use of the third method, the expected number was 37.4. The actual number was 3. Thus,

**TABLE 5.** EXPECTED AND ACTUAL NUMBERS OF BREAST CANCERS AMONG THE HIGH-RISK WOMEN WHO UNDERWENT PROPHYLACTIC MASTECTOMY.\*

	EVENTS IN SISTERS USED TO CALCULATE RATE		PERSON-YEARS OF FOLLOW-UP		BREAST CANCER		REDUCTION IN RISK (95% CI) percent
			SISTERS	PROBANDS	NO.	NO.	
					EXPECTED	OBSERVED	
All breast cancers (before and after prophylactic mastectomy) from age 18 to end of follow-up	Unadjusted	Adjusted†	13,336	2964	52.9	3	94.3 (83.5–98.8)
Breast cancer after prophylactic mastectomy to end of follow-up			3,109	2964	37.4	3	92.0 (76.6–98.3)

\*The expected incidence of breast cancer was calculated on the basis of a number of factors analyzed in the control group consisting of sisters of the probands. CI denotes confidence interval.

†The method of adjustment for ascertainment bias is described in the Methods section.

depending on the method used to calculate the expected rates, the reduction in the risk of breast cancer was 90 to 94 percent among the women with a high risk of cancer on the basis of family history.

**Death from Breast Cancer**

**Moderate-Risk Group**

The predicted incidence of death from breast cancer among the moderate-risk group was 10.4. The actual number was 0. Thus, the reduction in the risk of death was 100 percent (95 percent confidence interval, 70 to 100 percent).

**High-Risk Group**

When the data from the age of 18 to the end of follow-up were analyzed, there were 90 deaths from breast cancer among sisters. The expected numbers of deaths from breast cancer among the probands are shown in Table 6. Before adjustment for ascertainment bias, the expected number was 30.6. After adjustment, the number was 19.4. When the analysis included only sisters' deaths that followed the respective probands' prophylactic mastectomies, the number was 10.5. The actual number was 2. Thus, depending on the method used to calculate the expected rates, the reduction in the risk of death from breast cancer was 81 to 94 percent among the prophylactic-mastectomy group.

**Ovarian Cancer**

Ovarian cancer is a concern among women with a strong family history of breast cancer. In general, ovarian cancer appears later than breast cancer in such women. At the end of follow-up, two of the women in our high-risk group had ovarian cancer,

indicating that continuing follow-up for ovarian and other cancers is necessary for such women.

**DISCUSSION**

Prophylactic mastectomy is one option for preventing breast cancer in women at high risk for the disease, but the effectiveness of this procedure is unknown.<sup>4-6</sup> Thus, women contemplating prophylactic mastectomy must rely on expert opinions or decision models that use assumptions of the procedure's efficacy.<sup>4,13,14</sup> The ideal study would be a randomized clinical trial comparing prophylactic mastectomy with surveillance (or chemoprevention) in women of like risk. It is unlikely that high-risk women would agree to participate in such a study, given the substantial differences in management in the two groups. Moreover, even if such a study were feasible, it would require 10 to 20 years for adequate accrual and follow-up data to become available.

Therefore, we conducted a retrospective study of 639 women with a family history of breast cancer who underwent prophylactic mastectomy at our institution between 1960 and 1993. We found a statistically significant reduction in the incidence of breast cancer and of death from breast cancer after prophylactic mastectomy, as compared with the expected incidence in women with a family history who did not undergo the procedure.

Because ascertainment bias could lead to overestimates of the expected numbers of breast cancers, we calculated the incidence of breast cancer among the sisters in three ways: the first included all sisters with breast cancer, the second corrected for ascertainment bias, and the third included only sisters with breast cancer that occurred after the respective proband's

**TABLE 6.** EXPECTED AND ACTUAL NUMBERS OF DEATHS FROM BREAST CANCER AMONG THE HIGH-RISK WOMEN WHO UNDERWENT PROPHYLACTIC MASTECTOMY.\*

EVENTS IN SISTERS USED TO CALCULATE RATE	PERSON-YEARS OF FOLLOW-UP		DEATH FROM BREAST CANCER		
	SISTERS	PROBANDS	NO. EXPECTED	NO. OBSERVED	REDUCTION IN DEATHS (95% CI)  percent
All deaths from breast cancer from age 18 to end of follow-up					
Unadjusted	14,896	2970	30.6	2	93.5 (76.4–99.2)
Adjusted†	13,569	2970	19.4	2	89.7 (62.8–98.8)
Deaths from breast cancer after prophylactic mastectomy to end of follow-up	3,356	2970	10.5	2	80.9 (31.4–97.7)

\*The expected incidence of death from breast cancer was calculated on the basis of a number of factors analyzed in the control group consisting of sisters of the probands. CI denotes confidence interval.

†The method of adjustment for ascertainment bias is described in the Methods section.

prophylactic mastectomy. All approaches showed that prophylactic mastectomy was associated with a reduction in the incidence of breast cancer of at least 90 percent. Using a similar approach, we examined the risk of death from breast cancer among the probands and their sisters. The reduction in the risk of death from breast cancer ranged from 81 to 94 percent, depending on which deaths among the sisters were included in the analysis. These results show that there was a significant reduction in the incidence of breast cancer and of death from breast cancer among high-risk women after prophylactic mastectomy.

Among the 425 women with a moderate risk of breast cancer who underwent prophylactic bilateral mastectomy, the expected number of breast cancers according to the Gail model was 37.4 during the period of follow-up. The actual number was 4 (reduction in risk, 89.5 percent;  $P < 0.001$ ). There was a similar reduction in the risk of death from breast cancer. The Gail model was developed in a study of women who were screened regularly as part of the Breast Cancer Detection Demonstration Project. Other investigators have sought to validate the Gail model in different populations of patients. Bondy et al. evaluated the model prospectively in a cohort of white women with a family history of breast cancer.<sup>30</sup> They found that the model accurately predicted risk among women who followed screening guidelines but overestimated the risk among those who did not. Benichou and colleagues have also stated that the model may overestimate the risk in younger women who are not screened regularly.<sup>31</sup> We do not have data regarding our study participants' screening practices. We assumed that if they were concerned enough about breast cancer to undergo prophylactic mastectomy, they were also likely to have pursued regular screening.

Chemopreventive therapy — for example, with tamoxifen — is another prophylactic option for high-risk women. The National Surgical Adjuvant Breast and Bowel Project (NSABP) compared prophylactic tamoxifen with placebo and found that tamoxifen reduced the risk of invasive cancer by 49 percent during a median follow-up of 55 months.<sup>32</sup> Conversely, recent interim reports of two European trials showed that tamoxifen prophylaxis did not reduce the incidence of breast cancer significantly.<sup>33,34</sup> One of these studies was limited to women with a family history of breast cancer.<sup>33</sup> Possible explanations for these conflicting data include the use of different numbers of patients, differences in the age and risk levels of the study participants, differences in the lengths of follow-up, and the allowance of the use of hormone-replacement therapy in the European studies (used by 41 percent of women in the British trial<sup>33</sup> and 14 percent in the Italian study<sup>34</sup>). The larger number of patients in the NSABP trial and its prohibition of hormone-replacement therapy add to the strength of its

findings. However, unanswered questions about tamoxifen as a chemopreventive agent include the durability of its effect, its effect in carriers of *BRCA1* or *BRCA2* mutations, and its effect on the risk of death.

The duration of the protective effect of a prophylactic strategy is an important consideration for high-risk women. Our data show that the reduction in risk with prophylactic mastectomy persisted throughout the follow-up period (median, 14 years). Moreover, the majority of the cancers that did occur after prophylactic mastectomy were confined to the chest wall and were not associated with distant metastases. It will be important to continue to follow this cohort for additional cancers.

There are unique aspects to a single-institution study of a surgical procedure such as prophylactic mastectomy. First, because of the specialized nature of the subcutaneous mastectomy, women were referred to the Mayo Clinic specifically for the procedure, accounting for the large size of our cohort. Second, the procedures were performed by a limited number of surgeons, who used the same techniques. This factor is particularly important in an analysis of subcutaneous mastectomy, since there can be considerable variation in the amount of breast tissue that is retained.

The historical indications for prophylactic mastectomy have been broad and have included conditions that were not associated with a significantly increased risk of breast cancer.<sup>2</sup> The ability to predict risk, on the basis of both hereditary and nonhereditary factors, has improved in recent years,<sup>35-38</sup> and now the ability to identify women at very high risk on the basis of family history or genetic analysis should help ensure that this procedure is considered for the population at highest risk. Our high-risk group represents such a population.

There are limited data on women's perceptions and preferences regarding prophylactic mastectomy. Stefanek et al. studied a group of 164 high-risk women who were seen at the Breast Surveillance Service of Johns Hopkins Oncology Center from 1988 to 1992.<sup>39</sup> Each woman had at least one first-degree relative with breast cancer; 14 elected to undergo prophylactic mastectomy during the study period. The distinguishing features of the women who elected to undergo prophylactic surgery were higher subjective estimates of risk, a greater number of prior breast biopsies, and higher scores on a worry scale. The mean number of first-degree relatives with breast cancer did not differ significantly between these women and the women who chose not to undergo prophylactic mastectomy (1.4 vs. 1.0).

Many factors contribute to a high-risk woman's choice of a course of action: her objective risk of breast cancer; clinical features, such as the consistency of breast tissue and the resultant ease of examination; breast density on mammography; personal characteristics, including her experience with cancer within

her family; her role and responsibilities in her own nuclear family; her values; her experiences with the medical system; and her subjective assessment of risk. Before a high-risk woman undergoes prophylactic mastectomy, efforts must be made to correct any overestimates of risk and to allay excessive anxiety, and the woman should be encouraged to take her time to consider a decision of this magnitude.

In our retrospective series, subcutaneous mastectomy was performed more commonly than it is today. With improved methods for reconstructing the breast and nipple after total mastectomy and the more complete removal of breast tissue with this procedure, total mastectomy is the procedure of choice today for the majority of women who have decided to pursue prophylactic mastectomy because they have a high risk of breast cancer.

We found a significant reduction in the incidence of breast cancer and of death from breast cancer after prophylactic mastectomy, even among women at very high risk. In clinical decision making, the significant reduction in risk associated with the procedure must be weighed against other factors, including the need for breast reconstruction (which most women elect to undergo), the effect of the surgery on a woman's body image and sexuality, the irreversibility of the decision, and the realization that breast cancer would not have developed in all the women who undergo the procedure.

Supported in part by grants from the Department of Defense (DAMD 17-94-J-4216) and the National Cancer Institute (U10 CA37404-13) and by the Donaldson Charitable Trust.

*We are indebted to the participants in the study for their help in addressing an important and controversial topic; to Drs. Jeff Abrams, Ed Corn, Mark Greene, Noralane Lindor, and Ping Yang for suggestions regarding the study design; to Ms. Ann Harris and members of the Survey Research Center for follow-up of the patients; to Mr. Randy Vrabel, Mr. John Hermans, and Mr. Jeff Slezak for data analysis; to Ms. Diane Sitta for data collection; and to Ms. Gail Prechel for assistance with the preparation of the manuscript.*

## REFERENCES

- Lopez MJ, Porter KA. The current role of prophylactic mastectomy. *Surg Clin North Am* 1996;76:231-42.
- Pennisi VR. Redefined indications for subcutaneous mastectomy in patients with benign breast disease. *Aesthetic Plast Surg* 1986;10:101-4.
- Prophylactic mastectomy. Arlington Heights, Ill.: American Society of Plastic and Reconstructive Surgeons, June 1994.
- Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. *BRCA1* and *BRCA2*. *JAMA* 1997;277:997-1003.
- Statement of the American Society of Human Genetics on genetic testing for breast and ovarian cancer predisposition. *Am J Hum Genet* 1994; 55:i-iv.
- Hoskins KF, Stopfer JE, Calzone KA, et al. Assessment and counseling for women with a family history of breast cancer: a guide for clinicians. *JAMA* 1995;273:577-85.
- Hicken NF. Mastectomy: clinical pathologic study demonstrating why most mastectomies result in incomplete removal of mammary gland. *Arch Surg* 1940;40:6-14.
- Ziegler LD, Kroll SS. Primary breast cancer after prophylactic mastectomy. *Am J Clin Oncol* 1991;14:451-4.
- Eldar S, Meguid MM, Beatty JD. Cancer of the breast after prophylactic subcutaneous mastectomy. *Am J Surg* 1984;148:692-3.
- Goodnight JE Jr, Quagliana JM, Morton DL. Failure of subcutaneous mastectomy to prevent the development of breast cancer. *J Surg Oncol* 1984;26:198-201.
- Pennisi VR, Capozzi A, Perez FM. Subcutaneous mastectomy data: a preliminary report. *Plast Reconstr Surg* 1977;59:53-6.
- Pennisi VR, Capozzi A. Subcutaneous mastectomy data: a final statistical analysis of 1500 patients. *Aesthetic Plast Surg* 1989;13:15-21.
- Schrag D, Kuntz KM, Garber JE, Weeks JC. Decision analysis — effects of prophylactic mastectomy and oophorectomy on life expectancy among women with *BRCA1* or *BRCA2* mutations. *N Engl J Med* 1997; 336:1465-71.
- Grann VR, Panageas KS, Whang W, Antman KH, Neugut AI. Decision analysis of prophylactic mastectomy and oophorectomy in *BRCA1*-positive or *BRCA2*-positive patients. *J Clin Oncol* 1998;16:979-85.
- Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989;81:1879-86.
- Statement of the American Society of Clinical Oncology: genetic testing for cancer susceptibility, adopted on February 20, 1996. *J Clin Oncol* 1996;14:1730-6.
- Understanding gene testing. Bethesda, Md.: National Cancer Institute, December 1995. (NIH publication no. 96-2905.)
- Olopade OI, Cummings S. Genetic counseling for cancer: PPO Update 1996;10:1-13.
- Woods JE. Subcutaneous mastectomy: current state of the art. *Ann Plast Surg* 1983;11:541-50.
- Idem*. Breast reconstruction: current state of the art. *Mayo Clin Proc* 1986;61:579-85.
- Bilimoria MM, Morrow M. The woman at increased risk for breast cancer: evaluation and management strategies. *CA Cancer J Clin* 1995;45: 263-78.
- Leviton M, Montagu A. Textbook of human genetics. 2nd ed. rev. New York: Oxford University Press, 1977:410.
- Sham P. Statistics in human genetics. New York: John Wiley, 1997:32.
- Ernst VL. Epidemiology and natural history of ductal carcinoma in situ. In: Silverstein MJ, ed. Ductal carcinoma in situ of the breast. Baltimore: Williams & Wilkins, 1997:23-33.
- Fonseca R, Hartmann LC, Petersen IA, Donohue JH, Crotty TB, Givold JJ. Ductal carcinoma in situ of the breast. *Ann Intern Med* 1997; 127:1013-22.
- Kosary CL, Ries LAG, Miller BA, Hankey BF, Harras A, Edwards BK, eds. SEER cancer statistics review, 1973-1992: tables and graphs. Bethesda, Md.: National Cancer Institute, 1995. (NIH publication no. 96-2789.)
- United States life tables: 1959-61. Vol. 1. No. 1. Washington, D.C.: Government Printing Office, December 1964. (PHS publication no. 1252.)
- U.S. decennial life tables for 1969-71. Vol. 1. No. 2. Washington, D.C.: Government Printing Office, 1970. (DHHS publication no. (PHS) 75-1150.)
- U.S. decennial life tables for 1979-81. Vol. 1. No. 4. Washington, D.C.: Government Printing Office, 1980. (DHHS publication no. (PHS) 87-1150-4.)
- Bondy ML, Lustbader ED, Halabi S, Ross E, Vogel VG. Validation of a breast cancer risk assessment model in women with a positive family history. *J Natl Cancer Inst* 1994;86:620-5.
- Benichou J, Gail MH, Mulvihill JJ. Graphs to estimate an individualized risk of breast cancer. *J Clin Oncol* 1996;14:103-10.
- Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;90:1371-88.
- Powles T, Eccles R, Ashley S, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. *Lancet* 1998;352:98-101.
- Veronesi U, Maisonneuve P, Costa A, et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. *Lancet* 1998;352:93-7.
- Couch FJ, DeShano ML, Blackwood MA, et al. *BRCA1* mutations in women attending clinics that evaluate the risk of breast cancer. *N Engl J Med* 1997;336:1409-15.
- Schaid DJ. Re: probability of carrying a mutation of breast-ovarian cancer gene *BRCA1* based on family history. *J Natl Cancer Inst* 1997;89:1632-4.
- Berry DA, Parmigiani G, Sanchez J, Schildkraut J, Winer E. Probability of carrying a mutation of breast-ovarian cancer gene *BRCA1* based on family history. *J Natl Cancer Inst* 1997;89:227-38.
- Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer: implications for risk prediction. *Cancer* 1994; 73:643-51.
- Stefanek ME, Helzlsouer KJ, Wilcox PM, Houn F. Predictors of and satisfaction with bilateral prophylactic mastectomy. *Prev Med* 1995;24:412-9.