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ORIGINAL REPORT

Efficacy of Prophylactic Mastectomy in Women With Unilateral Breast Cancer: A Cancer Research Network Project

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ABSTRACT

Purpose
We investigated the efficacy of contralateral prophylactic mastectomy (CPM) in reducing contralateral breast cancer incidence and breast cancer mortality among women who have already been diagnosed with breast cancer.

Methods
This retrospective cohort study comprised approximately 50,000 women who were diagnosed with unilateral breast cancer during 1979 to 1999. Using computerized data confirmed by chart review, we identified 1,072 women (1.9%) who had CPM. We obtained covariate information for these women and for a sample of 317 women who did not undergo CPM.

Results
The median time from initial breast cancer diagnosis to the end of follow-up was 5.7 years. Contralateral breast cancer developed in 0.5% of women with CPM, metastatic disease developed in 10.5%, and subsequent breast cancer developed in 12.4%; 8.1% died from breast cancer. Contralateral breast cancer developed in 2.7% of women without CPM, and 11.7% died of breast cancer. After adjustment for initial breast cancer characteristics, treatment, and breast cancer risk factors, the hazard ratio (HR) for the occurrence of contralateral breast cancer after CPM was 0.03 (95% CI, 0.006 to 0.13). After adjustment for breast cancer characteristics and treatment, the HRs for the relationship of CPM with death from breast cancer, with death from other causes, and with all-cause mortality were 0.57 (95% CI, 0.45 to 0.72), 0.78 (95% CI, 0.57 to 1.06), and 0.60 (95% CI, 0.50 to 0.72), respectively.

Conclusion
CPM seems to protect against the development of contralateral breast cancer, and although women who underwent CPM had relatively low all-cause mortality, CPM also was associated with decreased breast cancer mortality.

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INTRODUCTION

Although bilateral prophylactic mastectomy in high-risk women reduces subsequent breast cancer occurrence by at least 95%,[1-3] the role of contralateral prophylactic mastectomy (CPM) in women with prior breast cancer is unclear. Each year in the United States, approximately 180,000 women develop unilateral breast cancer.[4] Two studies among women with prior unilateral breast cancer found that CPM decreased the risk of contralateral breast cancer but did not examine breast cancer–specific mortality.[5,6] It is important to determine the influence of CPM on the prognosis of women with breast cancer. We conducted a retrospective cohort study of women with unilateral breast cancer to determine the efficacy of CPM in reducing the incidence of contralateral

breast cancer occurrence and breast cancer death. The study was conducted among six members of the Cancer Research Network, which is a consortium of geographically dispersed research organizations based in health maintenance organizations (HMOs) funded by the National Cancer Institute (Bethesda, MD) to conduct cancer control research.

METHODS

Setting and Design Overview

Six HMOs of the Cancer Research Network collaborated on the study (Group Health Cooperative, Washington; Harvard Pilgrim Health Care, Massachusetts; HealthPartners, Minnesota; and three Kaiser Permanente regions: Northwest, Northern California, and Southern California). The combined enrollment of these HMOs in 1998 was approximately 7.5 million persons. Each of the six participating institutions obtained institutional review board approval.

This cohort study included all women who were identified as having had CPM, documenting through computerized data and chart review the percentage of women with subsequent contralateral breast cancer, subsequent breast cancer regardless of site, metastatic breast cancer, and death. To determine the efficacy of CPM, we used two different statistical methods, one to examine contralateral breast cancer occurrence and a different one to examine breast cancer mortality (Fig 1).

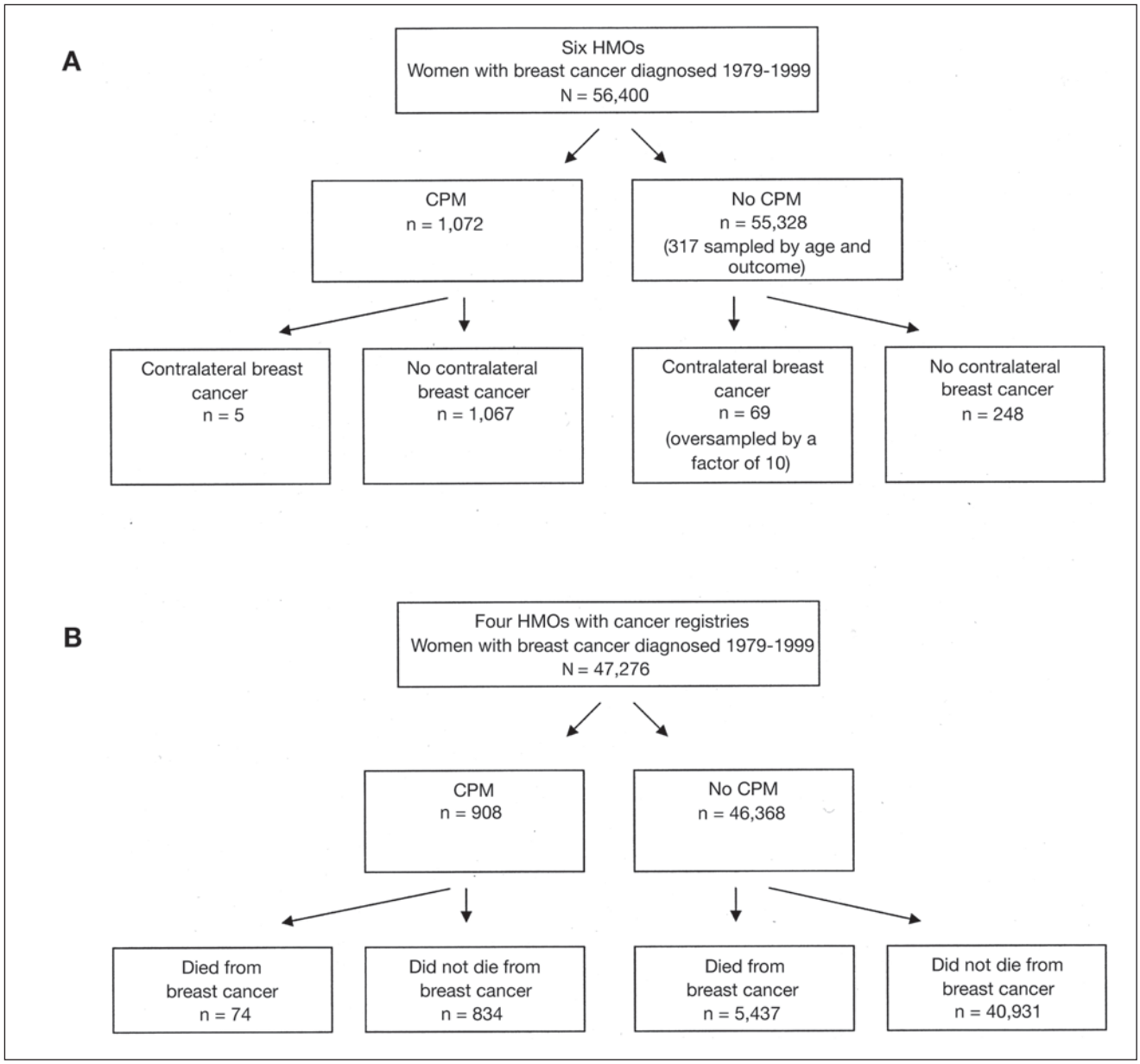

Fig 1. Study population and sampling. (A) Women assessed for occurence of contralateral breast cancer (computerized data and chart review). (B) Women assessed for breast cancer mortality (computerized data only). HMOs, health maintenance organizations; CPM, contralateral prophylactic mastectomy.

In determining the effect of CPM on contralateral breast cancer occurrence, we sought to adjust our analyses for covariates, such as breast cancer risk factors, disease characteristics, and treatments, that could be obtained by chart review. We used a case-cohort design that uses oversampling to maintain the power of the study while reducing the cost of collecting this detailed covariate information. We sampled all of the women with CPM. In addition, we oversampled women with breast cancer who did not undergo CPM but who developed contralateral breast cancer. If we had not oversampled these women, we would have needed to collect detailed information on nearly 10 times the number of women without CPM to get the same number who had a contralateral breast cancer occurrence. To correct for oversampling in the design, we used a weighted analysis where the weights were the inverse of the probability of being sampled. This unbiased method reduced data collection costs while maintaining statistical efficiency.

To determine the effect of CPM on breast cancer mortality, we used an ordinary cohort study design, including the entire cohort of women in four of the study sites and obtaining information on death from available Surveillance, Epidemiology, and End Results and institutional cancer registries. This method did not use covariate information from the chart and did not require oversampling or a weighted analysis.

Population

Female HMO members with a first breast cancer diagnosed at age 18 to 79 years during 1979 to 1999 (1981 to 1999 at one site) were potentially eligible for the study. To identify potential subjects, we used computerized data, including hospitalization (to identify women with a CPM), cancer registry (four sites), and electronic ambulatory care (two sites) data. Chart review was then used to determine final eligibility. We excluded women diagnosed with bilateral or metastatic breast cancer diagnosed either initially or within 60 days, to allow time for work-up of the extent of disease, because these women would be ineligible for a CPM. We further excluded women with unknown extent of disease or no surgical treatment.

Selection of Women With CPM

CPM was defined as subcutaneous mastectomy or a more extensive procedure performed to prevent breast cancer. To ascertain women who had undergone CPM during 1979 to 1999, we linked hospitalization data identifying women having a mastectomy (International Classification of Disease, 9th edition, codes 85.33-85.36, and 85.41-48) with cancer registry data. Women with a unilateral mastectomy procedure without a concurrent diagnosis of breast cancer and women coded with a bilateral mastectomy (because the code for bilateral mastectomy often is used incorrectly for unilateral mastectomy) were identified as having a possible CPM. The contralateral mastectomy procedure was considered as prophylactic only when the note accompanying the doctor's order in the chart mentioned "breast cancer prevention," "family history," "suspicious but benign" radiologic or pathologic findings, or "high risk." Computerized linkage with cancer registry data identified 2,261 women with a possible CPM, of whom 1,057 (47%) were determined to have had CPM through chart review, with most of the remaining women having had second therapeutic mastectomy (Table 1). In addition, 15 women who had been sampled for the non-CPM group were found to have an eligible CPM during chart review. Thus, we identified 1,072 eligible women with CPM.

Selection of Women Without CPM to Determine Effect of CPM on Breast Cancer Mortality

Women with a history of breast cancer who had not undergone CPM were potentially eligible for the comparison group. For the evaluation of breast cancer mortality, we evaluated all eligible women who were identified with a first breast cancer diagnosed at age 18 to 79 years during 1979 to 1999 (1988 to 1999 at one site) from the cancer registries available at the four HMOs with cancer registries (n = 46,368).

Selection of Women Without CPM to Determine Effect of CPM on Contralateral Breast Cancer

We used a case-cohort design to increase statistical efficiency by oversampling unexposed group members with the outcome of interest,[7] and therefore, we oversampled women without CPM

Table 1. Eligibility of Women With and Without CPM Sampled From Computerized Records for the Evaluation of Contralateral Breast Cancer From 1979 to 1999

Eligibility	No. of Women	
	CPM	Non-CPM
No. initially sampled	2,261	536
CPM status reclassified after record review	1,060	17
Unavailable medical record	73	35
Bilateral breast cancer, bilateral mastectomy, or metastatic breast cancer at initial breast cancer diagnosis	34	26
Unknown stage of initial breast cancer	16	4
Initial breast cancer not surgically treated	9	2
No personal history of breast cancer	5	18
Key date missing	5	1
Male	1	0
Sampled into the wrong stratum, and random number larger than the desired sampling frequency for the correct stratum	0	127
Subtotal eligible	1,057	306
CPM status reclassified after record review and subject eligible	15	11
Total eligible	1,072	317

Abbreviation: CPM, contralateral prophylactic mastectomy.

who subsequently developed a contralateral breast cancer. We then took the oversampling into account in the analysis. To do this, we used computerized data from a large HMO to establish sampling frequencies for women without CPM who did and did not develop a contralateral breast cancer. For women who did not develop a contralateral breast cancer, we sought to sample 0.5% of women born before 1945 and 1% of women born during or after 1945; and for women who developed a contralateral breast cancer, we sought to sample 5% and 10%, respectively. We then assigned each of the comparison women a random number from 0 to 1,000, and women whose random numbers were smaller than the desired sampling frequency for their stratum were selected for the chart review. Thus, a younger woman who developed a contralateral breast cancer was included in the study if her random number was less than 100 (ie, 10% of 1,000). Because women who did and did not develop a contralateral breast cancer were sampled at different frequencies, it is inappropriate to directly compare their proportions without first adjusting the results according to the sampling scheme.

CPM, contralateral breast cancer, and birth year were confirmed during chart review, and women who had been classified into the wrong stratum on the basis of incomplete computerized data were moved into the correct stratum only if they met the sampling criteria for that stratum, including the criterion that their random number be sufficiently low; otherwise, they were excluded. The predetermined sampling frequencies yielded 536 non-CPM subjects, of whom 306 were eligible after chart review (Table 1). In addition, 11 women sampled as having CPM, in fact, did not have CPM and were eligible for the comparison group, making a total of 317 women.

Data Collection

Data sources included computerized HMO databases, medical charts, and, for four sites, cancer registry and state mortality files. Thirteen chart reviewers abstracted data after an extensive training period using a training video, standardized coding manual, and regular conference calls with the lead author (L.J.H.). For each abstractor, quality control was assessed monthly by having a second abstractor review one of the initial abstractor's completed charts; we noted differences in the interpretation of the data for 5.9% of the data fields. Often, these differences related to the dates of events, so that the abstractors would differ from each other by several days. Women with unclear CPM status were discussed during meetings to minimize misinterpretation of this key variable.

Information on the initial breast cancer diagnosis included the histologic type, tumor size, stage, lymph node involvement, and scope of surgery and adjuvant therapy (chemotherapy, radiation therapy, and hormonal therapy). In addition, the date, type, and reason for each breast surgery were obtained from chart review. Possible reasons for breast surgery included a concurrent or prior breast cancer diagnosis, a positive family history of breast or ovarian cancer, radiologic findings of suspicious but benign microcalcifications, benign pathologic findings, and high-risk indications that were not specified.

For the evaluation of contralateral breast cancer risk, information on potentially confounding breast cancer risk factors was obtained from the medical chart. Contralateral breast cancer occurrence was determined from available cancer registries and computerized outpatient data and by chart review. For the evaluation of breast cancer mortality, only information that could be obtained from the cancer registries was used. Cause of death was obtained from cancer registry data, which were linked to the state mortality files.

Outcomes

Follow-up began on the diagnosis date of the initial breast cancer. For the evaluation of contralateral breast cancer, follow-up ended on the earliest date of a diagnosis of contralateral breast cancer; December 31, 1999; the woman's 80th birthday; or the date of death or disenrollment from the HMO. Contralateral breast cancers diagnosed within 60 days of CPM (n = 25) were considered to be incidental to the CPM and not counted as outcomes because it was the CPM that led to the cancer detection. However, these women were observed for a new contralateral breast cancer occurrence. For the evaluation of breast cancer mortality, follow-up ended on the date of death or the date of last contact, whichever occurred first, as recorded in cancer registries.

Data Analysis

We first examined the CPM group, evaluating time from CPM to contralateral breast cancer, any subsequent breast cancer (new primary or recurrent), metastatic breast cancer, and breast cancer death using a Kaplan-Meier plot. We evaluated time from CPM rather than time from initial breast cancer diagnosis because the timing of CPM after breast cancer diagnosis varied somewhat (median time, 3 months from diagnosis), and we could not display the timing in the Kaplan-Meier plot. We then compared the risks of contralateral breast cancer and breast cancer death among women who underwent CPM with the risks among women who did not undergo CPM using Cox proportional hazards regression. Analysis of each outcome was stratified by age group and HMO, and CPM was fitted as a time-dependent covariate.

For the analysis of contralateral breast cancer, we adjusted for characteristics of the initial breast cancer and treatment as well as potential confounders including family history of breast or ovarian cancer and number of breast cancer risk factors. Family history was time dependent, and chart notes of family history were not used until the date they were recorded. Because women without CPM who developed contralateral breast cancer were oversampled, it was essential that the analysis also took into consideration the sampling plan. We can correct for the oversampling when analyzing the time to occurrence of a new primary breast cancer because the sampling was by outcome. However, it precludes significance testing of differences in covariates between women with CPM versus women without CPM because of the difference in sampling methods. For time to diagnosis of a new primary breast cancer, we obtained an unbiased estimate of the hazard ratio (HR) with appropriate SEs by using a variant of the methodology developed for a standard case-cohort analysis with a robust covariance matrix.[7,8] This methodology included adjusting for differences of all examined covariates. The data were analyzed using SAS procedure PHREG (Version 8.2; SAS Institute, Cary, NC) with an offset to accommodate the sampling probabilities and an empirical sandwich estimator of the covariance matrix.

For the analysis of breast cancer mortality, characteristics of the initial breast cancer and treatment that were available in the cancer registries were included. Because all women who had an initial breast cancer recorded in the cancer registries were included in the analysis and, thus, no sampling plan was involved, a standard Cox proportional hazards regression was used.

RESULTS

Women With Unilateral Breast Cancer Who Underwent CPM

From 1979 to 1999, 56,400 women were diagnosed with breast cancer and were eligible for CPM according to

our criteria; 1.9% of these women (1,072) underwent CPM. The median time from the initial diagnosis to CPM was 3 months, and 47 women (4.4%) underwent the CPM after an ipsilateral breast cancer recurrence.

Characteristics of the Women

Table 2 shows descriptive characteristics for women who underwent CPM versus women who did not. Women who underwent CPM seemed to be younger at initial diagnosis, disproportionately white, and more likely to have had a family history of breast or ovarian cancer and seemed to have more risk factors for breast cancer than women without CPM. The extent of the initial disease was similar in the two groups, but more women with CPM had tumors that were greater than 2 cm and initially underwent mastectomy, whereas fewer women with CPM received adjuvant therapy. Because the study was not designed to test these differences, but only the outcomes in these two groups, we cannot show *P* values in the table.

The median length of follow-up from the initial breast cancer diagnosis was 5.7 years in women who underwent CPM and 4.8 years in women who did not. By the end of follow-up, 15% of women had disenrolled from their HMO.

Outcomes Among Women With CPM

Of the 1,072 women who underwent CPM among the six HMOs, 133 (12.4%) were diagnosed with a new or recurrent breast cancer 60 days or more after CPM, five (0.5%) developed a contralateral breast cancer, 112 (10.5%) developed metastatic disease, and 77 died of breast cancer during the follow-up period (Fig 2). Initial staging and treatment of these 133 women were as follows: 127 women had been diagnosed with invasive disease (local, n = 39; and regional, n = 88); 125 women had been treated with mastectomy, and eight had been treated with lumpectomy (followed by mastectomy at the time of their CPM); and 95 women had received chemotherapy, 54 had received hormone therapy, 44 had received radiotherapy, and 22 had received no adjuvant therapy. Among the 25 women who were diagnosed with incidental contralateral breast cancer within 60 days of their CPM, two developed subsequent breast cancer; one woman developed ipsilateral breast cancer 3 years after CPM, and one woman developed regional lymph node involvement 9 years after CPM. Neither woman had died by the end of the study.

Efficacy of CPM in Preventing Contralateral Breast Cancer

Among 1,072 women who underwent CPM among the six HMOs, five (0.5%) developed a contralateral breast cancer. Among women who did not undergo CPM, we oversampled those women who developed a contralateral breast cancer, obtaining 69 such women from the sample of 317 or 2.7% of the underlying population. After taking into account the sampling frequencies and adjusting for characteristics of the initial breast cancer and breast cancer risk factors in the multivariable analysis, the HR for contralateral breast cancer associated with CPM was 0.03 (95% CI, 0.006 to 0.13; Table 3). Risk of contralateral breast cancer was lower among women whose initial breast cancer was diagnosed in recent years. Women with four or more positive regional lymph nodes were at 15-fold higher risk than women with in situ disease (HR = 15.2; 95% CI, 2.2 to 104; Table 3). Risk tended to increase with the woman's age and the number of breast cancer risk factors, but the associations were not statistically significant. Initial lumpectomy (HR = 0.1; 95% CI, 0.03 to 0.58) and chemotherapy (HR = 0.3; 95% CI, 0.1 to 1.0) were associated with lower risk of contralateral breast cancer, whereas radiation therapy (HR = 3.1; 95% CI, 0.9 to 11) was associated with increased risk.

Efficacy of CPM in Preventing Breast Cancer Mortality

Among the four HMOs used in the mortality analysis, 74 (8.1%) of 908 women in the CPM group and 5,437 (11.7%) of 46,368 women in the non-CPM group died of breast cancer. The HR for breast cancer death was 0.57 (95% CI, 0.45 to 0.72) after adjustment for HMO, age, year, breast cancer characteristics, and treatment characteristics (Tables 4 and 5). Overall, 118 (13.0%) of 908 CPM women and 9,971 (20.5%) of 46,368 non-CPM women died during the study (HR = 0.60; 95% CI, 0.50 to 0.72). The number of women who died from known causes other than breast cancer was 42 (4.6%) in the CPM group and 4,040 (8.7%) in the non-CPM group (HR = 0.78; 95% CI, 0.57 to 1.06). Cause of death could not be ascertained for a small group of women, and for this group, the HR was 0.19 (95% CI, 0.05 to 0.78). When deaths from unknown causes were combined with deaths from known causes other than breast cancer, the HR decreased from 0.78 to 0.69 (95% CI, 0.51 to 0.93).

Breast cancer mortality was lowest among women initially diagnosed between the ages of 40 and 49 years and decreased with year of diagnosis (Table 5). Women with regional breast cancer had a 10-fold higher risk of dying than women with in situ disease (HR = 10.4; 95% CI, 8.2 to 13). Initial lumpectomy (HR = 0.70; 95% CI, 0.64 to 0.76) and hormonal therapy (HR = 0.77; 95% CI, 0.72 to 0.82) were associated with a lower risk of dying, whereas chemotherapy (HR = 1.4; 95% CI, 1.3 to 1.5) was associated with increased risk.

DISCUSSION

Among 1,072 women with a history of unilateral breast cancer who underwent CPM, 12.4% developed a subsequent breast cancer, 0.5% developed a contralateral breast

Table 2. Characteristics of Women With and Without CPM After Unilateral Breast Cancer, 1979-1999

Characteristic		% of Women	
		CPM (n = 1,072)	Non-CPM* (n = 317)
Age at initial breast cancer, years			
Mean	50	58	
Range	26-78	27-79	
HMO			
Group Heath Cooperative		9	9
Harvard Pilgrim Heath Care		2	6
HealthPartners		5	2
Kaiser Permanente, Northern California		33	39
Kaiser Permanente Northwest		11	9
Kaiser Permanente Southern California		40	35
Race			
White		85	72
African American		4	8
Hispanic		5	5
Asian/Pacific Islander		3	8
Native American		0	0
Other/unknown		3	7
First- and second-degree family history of breast or ovarian cancer			
Adopted		1	0
No note		27	30
None		37	51
One second-degree relative		7	5
One first-degree or two second-degree relatives†		15	10
≥ Two first-degree or ≥ two multigeneration relatives†		13	4
History of benign breast biopsy			
0		74	78
1		17	16
2†		6	5
3†		2	0
4+†		1	1
History of atypical hyperplasia			
No		96	98
Yes†		4	2
History of LCIS			
None		99	99
Unilateral†		1	0
Bilateral†		0	1
History of ovarian cancer			
Yes†		0	1
No		99	98
Unknown		1	1
First birth after age 30 years			
Nulliparous†		14	13
Yes†		13	12
No		61	54
Unknown		12	21
Total No. of breast cancer risk factors			
0		47	58
1		39	37
2+		14	5
Follow-up to end of study			
< 1 year		3	5
1-5 years		42	46
5.1-10 years		35	36
10.1-15 years		14	11
15.1-20 years		6	2

(continued on following page)

Table 2. Characteristics of Women With and Without CPM After Unilateral Breast Cancer, 1979-1999 (continued)

Characteristic	% of Women	
	CPM (n = 1,072)	Non-CPM* (n = 317)
Time to CPM after initial breast cancer diagnosis		
< 1 month	29	—
1-4 months	24	—
> 4 months, < 1 year	18	—
1-5 years	24	—
5-15 years	5	—
Diagnosis year		
1979-1984	12	7
1985-1989	18	21
1990-1994	35	40
1995-1999	35	32
Extent of disease		
In situ, noninfiltrating	18	13
Localized	50	58
Regional	32	29
Tumor size		
≤ 2 cm	59	66
> 2 cm	32	23
Unknown	9	11
Initial treatment		
Lumpectomy	5	47
Alone	2	5
With radiation only	1	13
With radiation and hormone therapy	0	12
With radiation and chemotherapy	1	6
With radiation, hormone therapy, and chemotherapy	1	7
Other combinations	0	4
Mastectomy	95	53
Alone	35	19
With chemotherapy only	19	5
With hormone therapy only	14	13
With chemotherapy and hormone therapy	16	7
With chemotherapy and radiation	3	3
With chemotherapy, hormone therapy, and radiation	6	5
Other combinations	2	1

Abbreviations: CPM, contralateral prophylactic mastectomy; HMO, heath maintenance organization; LCIS, lobular carcinoma-in-situ.
*Calculated by weighting women who developed contralateral breast cancer by a factor of 10 relative to women who did not develop contralateral breast cancer to adjust for the case-cohort oversampling of women without CPM who developed a contralateral breast cancer. Estimates of these proportions are unbiased, but SEs and *P* values cannot be computed because of the sampling scheme.
†Used to compute total number of breast cancer risk factors.

cancer, and 10.5% developed metastases after CPM. The percentage of women who died of breast cancer was 8.1%. The risk of subsequent contralateral breast cancer was dramatically reduced by 97% in women who underwent CPM (HR = 0.03; 95% CI, 0.006 to 0.13) compared with similar women who did not undergo the procedure. Although the women who underwent CPM may have had lower mortality from causes other than breast cancer than women who did not undergo CPM (HR = 0.78; 95% CI, 0.57 to 1.06), their breast cancer mortality was even further reduced (HR = 0.57; 95% CI, 0.45 to 0.72). Therefore, overall, the procedure protected women against subsequent contralateral breast cancer occurrence and breast cancer mortality. These results took into account extent of disease, treatment characteristics, the woman's age, the year of breast cancer diagnosis, and, for the analysis of contralateral breast cancer risk, a family history of breast or ovarian cancer and the number of breast cancer risk factors.

To our knowledge, this is the first study to report the efficacy of CPM in preventing breast cancer death. The study included more than 1,000 women with CPM as well as appropriate comparison groups. By using computerized databases with a valid and efficient study design, we identified a large group of women who had undergone the procedure. In addition, the patients were drawn from community settings across a wide geographic area in five states.

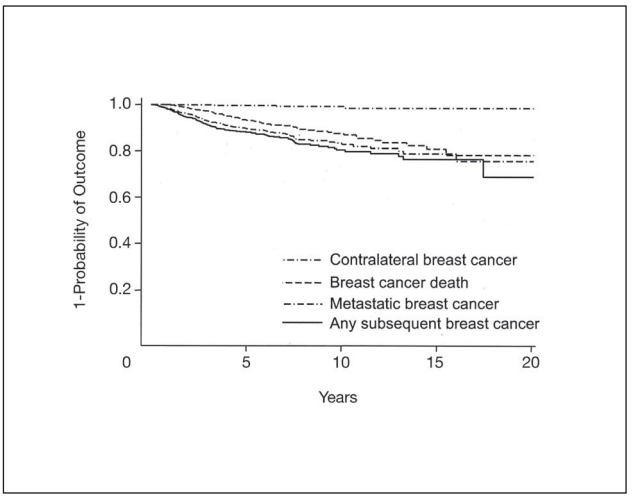

Fig 2. Time from contralateral prophylactic mastectomy (CPM) to each of the four breast cancer outcomes for 1,072 women with CPM: five with contralateral breast cancer, 77 with breast cancer death, 112 with metastatic breast cancer, and 133 with any subsequent breast cancer.

CPM reduces the risk of breast cancer occurrence and death by reducing the risk of development of new primary breast cancer. In addition, we found that CPM removed, before it was otherwise detected, breast cancer in the contralateral breast. However, the risk of metastatic breast cancer in locations other than the contralateral breast is not reduced by CPM. Therefore, it is not surprising that we found CPM to be less effective at preventing breast cancer mortality than preventing subsequent contralateral breast cancer. For the same reason, it is to be expected that the mortality reduction associated with CPM is less than the mortality reduction for bilateral prophylactic mastectomy.[1-3]

Prudent interpretation of this study requires consideration of its limitations. We identified five limitations that could have resulted in a protective effect of CPM being exaggerated or minimized. First, women who chose to undergo CPM may have been healthier than women who did not. One aspect of overall health is comorbidity, and women with CPM may have had less comorbidity than women without CPM (as evidenced by their 27% lower risk of death from causes other than breast cancer), and this may have reduced their apparent breast cancer mortality. Because the cancer registries do not collect information on comorbidity, we were unable to evaluate this possibility directly. However, two previous studies have examined the effect of comorbidity on mortality with breast cancer, observing that the increased mortality rate among women with comorbid conditions is focused almost exclusively on non–breast cancer–specific mortality. In a study of 13,358 breast cancer patients diagnosed at Kaiser Permanente Northern California and Group Health Cooperative during 1985 to 1992, patients with higher Charlson/Deyo comorbidity index scores had higher overall mortality (compared with comorbidity score = 0: score = 1, risk ratio [RR] = 1.7; and score = 2+, RR = 2.7) but similar breast cancer mortality (compared with score = 0: score = 1, RR = 1.1; and score = 2+, RR = 1.1).[9] Similarly, in a study of 936 women diagnosed with breast cancer in metropolitan Detroit, there was a relationship of the number of comorbidities with risk of death from causes other than breast cancer (compared with none: one comorbidity, RR = 2.9; two comorbidities, RR = 6.8; and three or more comorbidities, RR = 19.5) but not with risk of death from breast cancer (compared with none: one comorbidity, RR = 1.2; two comorbidities, RR = 1.4; and three or more comorbidities, RR = 1.2).[10] The associations were observed after adjustment for age, stage, and other covariates. These studies suggest that our findings for non–breast cancer–related mortality may be related to comorbidity and that this difference in comorbidity is unlikely to explain the observed difference in risk of death from breast cancer. Other than comorbidity, which has been assessed in past studies, we cannot comment on the role of other aspects of health as they relate to breast cancer mortality.

Second, it is possible that CPM women received higher quality treatment than women who did not undergo CPM. For example, women undergoing CPM may have been more likely to receive anthracycline chemotherapy, which is more effective than earlier chemotherapies. We did not obtain data on the chemotherapy agent used, but generally, we did not see evidence for differences in treatment in our data. As expected, CPM patients were more likely to undergo mastectomy than lumpectomy as initial treatment of their breast cancer (92% in CPM group *v* 53% in non-CPM group), and they were less likely to receive radiation (7% in CPM group *v* 26% in non-CPM group); thus, it was necessary to adjust for treatment in the analysis of efficacy. The proportions of patients who received chemotherapy (42% in CPM group *v* 39% in non-CPM group) or hormonal therapy (27% in CPM group *v* 34% in non-CPM group) were similar.

Third, we observed an inverse relationship between CPM and death from unknown cause. If a disproportionate number of non-CPM women whose deaths were coded as having unknown cause in fact died from breast cancer, we may have underestimated the protective effect of CPM. But, if these women died disproportionately from causes other than breast cancer, we would have overestimated the protective effect of CPM. However, because the cause of death was unknown for so few women, combining deaths of unknown cause with deaths of known cause other than breast cancer did not change our findings to an important degree.

Fourth, for the mortality analysis, we relied on tumor registry data for treatment. Although there has been concern expressed that registry information on adjuvant therapy is poor, a recent report gives evidence that the quality of chemotherapy data from HMOs is quite complete (88%).[11] Incomplete information on adjuvant therapy would make it

Table 3. Relationship of CPM and Other Factors to the Risk of Contralateral Breast Cancer in Multivariate Analysis*

Factor	Adjusted Hazard Ratio	95% CI
CPM		
No	1.0	—
Yes	0.03	0.006 to 0.13
Age at first breast cancer		
≤ 39 years	1.0	—
40-49 years	1.4	0.4 to 5.4
50-59 years	3.2	0.3 to 31
60-69 years	5.5	0.6 to 49
≥ 70 years	5.3	0.4 to 73
Year of initial breast cancer		
1979-1984	1.0	—
1985-1989	0.17	0.04 to 0.72
1990-1994	0.11	0.02 to 0.52
1995-1999	0.04	0.01 to 0.26
One first-degree, two second-degree, or more extensive family history of breast or ovarian cancer		
No	1.0	—
Yes	1.2	0.5 to 3.1
Total No. of breast cancer risk factors		
0	1.0	—
1	4.2	0.3 to 54
≥ 2	9.0	0.8 to 107
Extent of disease and nodal status of initial breast cancer		
In situ	1.0	—
Local	2.5	0.6 to 11
Regional, 1-3 nodes	5.5	1.0 to 31
Regional, 4+ nodes or direct extension	15.2	2.2 to 104
Tumor size		
≤ 2 cm	1.0	—
≥ 2 cm	0.7	0.3 to 2.0
Unknown	0.8	0.2 to 3.1
Surgery		
Mastectomy	1.0	—
Lumpectomy	0.1	0.03 to 0.58
Radiation therapy		
No	1.0	—
Yes	3.1	0.9 to 11
Chemotherapy		
No	1.0	—
Yes	0.3	0.1 to 1.0
Hormonal therapy		
No	1.0	—
Yes	1.1	0.5 to 2.7

Abbreviation: CPM, contralateral prophylactic mastectomy.
*All factors in the table were simultaneously adjusted for in a Cox proportional hazards model.
†From Table 2.

more difficult for us to observe a protective effect. Similarly, for the mortality analysis, we did not obtain data on breast cancer risk factors that may have differed between women who did and did not undergo CPM; whereas, for the analysis of contralateral breast cancer incidence, the data we obtained were somewhat incomplete for family history and age at first birth. If these risk factors were more common in women who underwent CPM, then we would have underestimated the efficacy of CPM.

Fifth, 15% of the study population disenrolled before the end of the study. Considering that the period of observation was as long as 20 years for some women, this is not surprising. Nonetheless, if the rate of disenrollment differed by CPM and by outcome (development of a contralateral breast cancer or breast cancer death), then we may have misestimated the protective effect of CPM. Although such a bias may have affected the study to some degree, it could not have resulted in the magnitude of protection that we observed.

As explained in Methods, we categorized breast cancers discovered at the time of CPM as incident and did not count them as outcomes because it was the CPM that led to the

Table 4. Mortality in Women With and Without CPM After Unilateral Breast Cancer in Multivariate Analysis

Cause of Death	CPM (n = 908) No.	CPM (n = 908) %	No CPM (n = 46,368) No.	No CPM (n = 46,368) %	Adjusted Hazard Ratio	95% CI
Breast cancer	74	8	5,437	12	0.57	0.45 to 0.72
Unknown	2	0.2	494	1	0.19	0.05 to 0.78
Other than breast cancer						
Include unknown	44	5	4,534	10	0.69	0.51 to 0.93
Exclude unknown	42	5	4,040	9	0.78	0.57 to 1.06
All causes						
Include unknown	118	13	9,971	22	0.60	0.50 to 0.72
Exclude unknown	116	13	9,477	20	0.62	0.52 to 0.75

NOTE. Hazard ratios adjusted for HMO, age at initial diagnosis of breast cancer, year of breast cancer diagnosis, stage, tumor size, surgery (lumpectomy, mastectomy), chemotherapy (yes, no), radiation therapy (yes, no), and hormonal therapy (yes, no).
Abbreviations: CPM, contralateral prophylactic mastectomy; HMO, health maintenance organization.

cancer detection. These women were observed for a new contralateral breast cancer occurrence. Of the 25 women with breast cancer discovered during the CPM procedure, 16 had the CPM procedure within 60 days of the initial breast cancer diagnosis. By our cohort definitions, women diagnosed with bilateral breast cancer within 60 days were excluded to ensure adequate work-up of the initial disease. This leaves nine women whose incidental breast cancer was diagnosed more than 60 days after the initial diagnosis. If we count these nine breast cancers as outcomes, then the protective effect of CPM is less strong but still highly significant (HR = 0.17; 95% CI, 0.06 to 0.45). However, we believe it is highly inappropriate to include these as outcomes because CPM clearly cannot prevent breast cancers that are already present at the time the surgery is performed, whereas removal of these breast cancers, through CPM, can prevent their progression to metastasis and death.

Generalizing our findings to other practice settings should be possible because the breast cancer survival of our patients seems similar to the survival observed nationally. In our cohort of women without CPM, we observed a survival rate of 90% after a median of 4.8 years of follow-up. This compares to a 5-year survival rate of 92% among women in the National Surveillance, Epidemiology, and End Results registry (1992 to 1997) after taking into consideration stage distribution.[12] However, our study included women with an initial breast cancer diagnosed during 1979 to 1999. Since then, there have been treatment changes that likely have reduced mortality among women who do not undergo CPM. Also, our study identified few women at very high risk for breast cancer, for whom we cannot comment on the efficacy of CPM.

Two earlier reports have examined the effect of CPM on subsequent contralateral breast cancer and found protective effects similar to our results. After a mean of 6.8 years of follow-up, Peralta et al[5] observed no contralateral breast cancers among 64 women who underwent CPM but found 36 contralateral breast cancers (19.8%) among 182 women who did not undergo CPM (HR = 0; 95% CI, 0 to 0.17). The disease-free survival rate was 55% in the CPM group versus 28% in the comparison group ($P = .01$), and the overall survival rate was 64% in the CPM group versus 49% in the comparison group ($P = .26$). The study did not report data on breast cancer mortality. McDonnell et al[6] observed 745 women with both a personal history of breast cancer and a family history of breast or ovarian cancer for a median 10 years of follow-up. Eight women (1.1%) were diagnosed with contralateral breast cancer, for a risk reduction of 94% when baseline risk was computed using the Anderson model (proportion expected, 17.9%); however, the study did not report on mortality.

Although our results compare well with these two earlier reports, the rate of occurrence of contralateral breast cancer in our study (2.7% among women without CPM) was lower than reported in those studies (19.8% and 17.9%). The rate we report is close to the rate reported in a national study of 72,000 Swedish women diagnosed during 1970 to 1996, among whom 3.5% developed contralateral breast cancer during an unspecified follow-up period.[13] Differences in rates among the three efficacy studies may have resulted from differences in the period of follow-up (4.8 years in the present study *v* 6.8 and 10 years), family history of breast cancer (19% in the present study *v* 46% and 100%), and use of adjuvant therapy (frequency of use was not reported in the two earlier studies).

We observed that approximately 2% of women with unilateral breast cancer according to our criteria undergo CPM. Most of these women (65%) had no recorded first- or second-degree family history of breast or ovarian

Table 5. Relationship of CPM and Other Factors to Breast Cancer Mortality in Multivariate Analysis*

Factor	Adjusted Hazard Ratio	95% CI
CPM		
No	1.0	—
Yes	0.57	0.45 to 0.72
Age at first breast cancer		
≤ 39 years	1.0	—
40-49 years	0.77	0.70 to 0.84
50-59 years	0.81	0.74 to 0.89
60-69 years	0.83	0.75 to 0.91
≥ 70 years	0.93	0.83 to 1.05
Year of initial breast cancer		
1979-1984	1.0	—
1985-1989	0.84	0.77 to 0.91
1990-1994	0.72	0.66 to 0.80
1995-1999	0.66	0.59 to 0.74
Extent of disease and nodal status of initial breast cancer		
In situ	1.0	—
Local	3.6	2.8 to 4.5
Regional	10.4	8.2 to 13
Tumor size		
≤ 2 cm	1.0	—
≥ 2 cm	2.2	2.1 to 2.4
Unknown	1.6	1.5 to 1.7
Surgery		
Mastectomy	1.0	—
Lumpectomy	0.70	0.64 to 0.76
Radiation therapy		
No	1.0	—
Yes	1.1	1.0 to 1.2
Chemotherapy		
No	1.0	—
Yes	1.4	1.3 to 1.5
Hormonal therapy		
No	1.0	—
Yes	0.77	0.72 to 0.82

Abbreviation: CPM, contralateral prophylactic mastectomy.
*All factors in the table were simultaneously adjusted for in a Cox proportional hazards model.

cancer. The frequency of CPM in other practices is not clear, but in the study by Peralta et al,[5] approximately 2.2% of patients underwent the procedure between 1973 and 1998. The Society of Surgical Oncology has indicated that CPM is justified in certain patients.[14] The procedure may be undertaken more often in practice than previously recognized. With increasing attention to bilateral prophylactic mastectomy in both the medical[1-3] and lay press, CPM procedures may further increase. Therefore, it is important to determine whether the procedure has a place in the management of breast cancer. Our results suggest that, for women and their doctors considering the effect of CPM, the procedure may have a role against contralateral breast cancer occurrence and death.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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