VOLUME 25 · NUMBER 33 · NOVEMBER 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Increasing Use of Contralateral Prophylactic Mastectomy for Breast Cancer Patients: A Trend Toward More Aggressive Surgical Treatment

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Submitted April 24, 2007; accepted August 21, 2007; published online ahead of print at www.jco.org on October 22, 2007.

Presented in part at the Annual Meeting of the Society of Surgical Oncology, Washington, DC, March 16, 2007.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/07/2533-5203/$20.00

DOI: 10.1200/JCO.2007.12.3141

ABSTRACT

Purpose
Many patients with unilateral breast cancer choose contralateral prophylactic mastectomy to prevent cancer in the opposite breast. The purpose of our study was to determine the use and trends of contralateral prophylactic mastectomy in the United States.

Patients and Methods
We used the Surveillance, Epidemiology and End Results database to review the treatment of patients with unilateral breast cancer diagnosed from 1998 through 2003. We determined the rate of contralateral prophylactic mastectomy as a proportion of all surgically treated patients and as a proportion of all mastectomies.

Results
We identified 152,755 patients with stage I, II, or III breast cancer; 4,969 patients chose contralateral prophylactic mastectomy. The rate was 3.3% for all surgically treated patients; 7.7%, for patients undergoing mastectomy. The overall rate significantly increased from 1.8% in 1998 to 4.5% in 2003. Likewise, the contralateral prophylactic mastectomy rate for patients undergoing mastectomy significantly increased from 4.2% in 1998 to 11.0% in 2003. These increased rates applied to all cancer stages and continued to the end of our study period. Young patient age, non-Hispanic white race, lobular histology, and previous cancer diagnosis were associated with significantly higher rates. Large tumor size was associated with a higher overall rate, but with a lower rate for patients undergoing mastectomy.

Conclusion
The use of contralateral prophylactic mastectomy in the United States more than doubled within the recent 6-year period of our study. Prospective studies are needed to understand the decision-making processes that have led to more aggressive breast cancer surgery.

J Clin Oncol 25:5203-5209. © 2007 by American Society of Clinical Oncology

INTRODUCTION

Women with unilateral breast cancer have a significantly increased risk of developing a second cancer in the contralateral breast. The annual incidence of contralateral breast cancer, about 0.5% to 0.75%, does not change with time.[1-6] In contrast, the peak hazard of systemic recurrence of unilateral breast cancer is 1 to 2 years after treatment; the risk decreases consistently after 2 to 5 years.[7] Thus, occurrence of contralateral breast cancer is clinically more significant in patients who are likely to survive for a long time.

Specific clinical and pathologic factors are associated with an increased risk of developing contralateral breast cancer[1,8-11] including: young patient age, a family history of breast cancer, lobular type histology, multicentric cancer, and previous chest radiation. Moreover, patients with unilateral breast cancer who also have *BRCA1* or *BRCA2* genetic mutations have a markedly increased risk of developing contralateral breast cancer.[12,13]

The fear of developing contralateral breast cancer leads some patients with unilateral breast cancer to consider contralateral prophylactic mastectomy (CPM). CPM significantly reduces the risk of contralateral breast cancer, but the procedure is more aggressive and irreversible; it is also unnecessary for preventing contralateral breast cancer in most patients.[14-17] Moreover, since the risk of systemic metastases often exceeds the risk of contralateral breast cancer, most patients will not experience any survival benefit. The purpose of our study was to evaluate, in a population-based cohort, the rate of and any trends toward CPM for patients with unilateral

breast cancer. Until our study, the rate of CPM in the United States had not been determined.

PATIENTS AND METHODS

Data

We used the Surveillance, Epidemiology and End Results (SEER) cancer registry public-use database to examine rates and trends of CPM in women with unilateral breast cancer from 1998 through 2003. The SEER cancer registries provide population-based cancer surveillance for 16 areas that represent approximately 26% of the United States.[18] Given the recent expansion of the SEER program, information covering our entire 6-year study period for 12 registries was available; for the remaining four registries, information was available only for 2000 through 2003. The information collected by SEER includes patient demographic characteristics, primary tumor site, tumor laterality, histology type, tumor stage, tumor grade, diagnostic confirmation, type of surgery, radiation, vital status (through December 31, 2003), and cause of death (as recorded on the death certificate).

Beginning with cancers diagnosed in 1998, the SEER site-specific surgery codes included contralateral mastectomy if it was planned as the first course of treatment for patients with unilateral breast cancer.[18] However, determining the rate of CPM was complicated by the available surgical choices that breast cancer patients were offered. Some patients (eg, those with large tumors) had only two realistic options: unilateral mastectomy or bilateral mastectomy (including CPM). Yet, most patients had three surgical options: breast-conserving surgery (BCS), unilateral mastectomy, or bilateral mastectomy (including CPM). Therefore, to capture the breadth of surgical options, we determined the overall rate of CPM-all (CPM-A; ie, proportion of all surgically treated patients who underwent CPM) and, in addition, the rate of CPM-mastectomy (CPM-M; ie, proportion of all mastectomy patients who underwent CPM) to exclude patients treated with BCS, since these patients generally did not undergo CPM.

Patients

We limited our study to women with invasive unilateral breast cancer (stages I, II, or III) treated with surgery. We excluded women who were diagnosed at age 17 or younger, age 80 or older, or only at the time of the death certificate or autopsy; women whose cancer was reported by a nursing home; those with in situ or unstaged tumors, multifocal disease, bilateral disease or disease of unknown laterality; those without microscopic confirmation of cancer; and those without data on tumor size, grade, or lymph node status. We also excluded patients with grade IV (undifferentiated, anaplastic) breast cancer because this grade is not commonly reported and this diagnosis may potentially represent nonbreast malignancies that may have metastasized to the breast. We also excluded women with multiple primary breast cancers diagnosed within the same month to ensure that the contralateral mastectomy was actually prophylactic. In addition, we excluded women who underwent radical or extended radical mastectomy. We further limited the cohort to women with ductal or lobular type histology who were not diagnosed with metastatic disease (stage IV). The specific surgery codes and step-wise ascertainment of our study cohort is listed in the Appendix Table A1 (online only).

We defined CPM as mastectomy surgery codes that included the comment "with removal of uninvolved contralateral breast." Lobular type histology was defined by any histologic evidence of lobular component. Tumor grade was classified as I and II versus III. Tumor size was categorized as follows: smaller than 1 cm, 1 to 1.9 cm, 2.0 to 4.9 cm, or $\geq$ 5 cm. Estrogen receptor (ER) status was defined as positive, negative, or unknown. Lymph node status was categorized as positive or negative.

Analysis

We compared demographic and tumor variables in women with unilateral breast cancer who underwent CPM, BCS, or unilateral mastectomy for each year of our 6-year study period (1998 through 2003). We used logistic regression models to test for significance. For each year, we assessed the rates of CPM-A (the proportion of all surgically treated patients who underwent CPM) and of CPM-M (the proportion of all mastectomy patients who underwent CPM). Using logistic regression, we modeled the use of CPM relative to all other surgically treated patients and relative to unilateral mastectomy patients. All models included the patients' age, race, year of diagnosis, previous history of nonbreast cancer diagnosis, cancer stage, tumor size, tumor grade, ER status, lymph node status, histology type, and registry. We confirmed that all patterns we observed persisted when we limited our analysis to the 12 SEER registries that contributed data across our entire 6-year study period.

All statistical analyses were completed using SAS software, version 9.1 (SAS Institute, Cary, NC). Because our study used preexisting data with no personal identifiers, the human subjects committee of the University of Minnesota's (Minneapolis, MN) institutional review board determined that it was exempt from review.

RESULTS

Over our 6-year study period (1998 through 2003), 152,755 women were diagnosed with unilateral breast cancer and treated with surgery. Most underwent either BCS (57.8%) or a unilateral mastectomy (38.9%), but 4,969 underwent CPM (CPM-A, 3.3%). Of those who underwent mastectomy, 7.7% (CPM-M) underwent CPM. Patient and tumor characteristics are presented in Table 1.

Logistic regression analysis (Table 2) demonstrated that young age was associated with significantly higher CPM-A and CPM-M rates: 6.7% of all surgically treated patients age 39 or younger underwent CPM, as compared with only 1.3% of women in their 70s. The CPM-A and CPM-M rates were also significantly higher among patients of non-Hispanic white race, among patients with a previous cancer diagnosis, and among patients with lobular histology. Larger tumor size was associated with a higher CPM-A rate, but with a lower CPM-M rate. In other words, patients with larger tumors were more likely to undergo bilateral mastectomy; however, among mastectomy patients, those with smaller tumors were more likely to choose CPM. Lower tumor grade and negative lymph node status were associated with a significantly higher CPM-M rate. ER status was not associated with either CPM-A or CPM-M. However, the CPM-M rate was significantly lower for patients with ER-unknown/not done status as compared with either ER-positive or ER-negative patients.

The CPM-A (Fig 1) and CPM-M (Fig 2) rates significantly increased for all stages of breast cancer. These trends continued to the end of our study period with no plateau effect. The CPM-A rate significantly increased from 1.8% in 1998 to 4.5% in 2003 (150% increase); similarly, the CPM-M rate significantly increased from 4.2% in 1998 to 11.0% in 2003 (162% increase). The CPM rates also significantly increased for both lobular and nonlobular histology (data not shown). The increased CPM rate occurred simultaneously with a continued increase in the BCS rate (1998, 56.1%; 2003, 59.7%) and a continued decrease in the unilateral mastectomy rate (1998, 42.0%; 2003, 35.9%).

We observed considerable geographic variation in CPM-A and CPM-M rates ($P < .0001$, 14 *df*; Table 3). For example, the CPM-A rate was lowest in the Connecticut registry (1.4%) and highest in metropolitan Atlanta (5.6%) and in Iowa (5.6%). The four registries that were added in 2000 had intermediate CPM-A rates (3.1% to 4.2%). We saw similar patterns in CPM-M rates. The CPM rates significantly increased from 1998 to 2003 for all registries except for Rural Georgia, which is exceptionally underpowered. We did not observe any obvious trends in CPM rates based on geographic location in the United States (east coast *v* west coast *v* midwest *v* south).

Table 1. Patient and Tumor Characteristics

Characteristic	CPM (CPM-A)		BCS		Unilateral Mastectomy		CPM-M* (%)
	No.	%	No.	%	No.	%	
No. of patients	4,969	3.3	88,326	57.8	59,460	38.9	7.7
Age, years							
18-39	631	6.7	4,694	49.6	4,136	43.7	13.2
40-49	1,602	5.1	17,610	56.4	12,011	38.5	11.8
50-59	1,510	3.6	25,371	60.7	14,916	35.7	9.2
60-69	794	2.2	21,855	59.9	13,853	37.9	5.4
70-79	432	1.3	18,796	55.6	14,544	43.1	2.9
Race/ethnicity							
Non-Hispanic white	4,278	3.7	68,641	59.2	43,079	37.1	9.0
Hispanic	250	2.1	6,605	54.0	5,366	43.9	4.5
Non-Hispanic black	222	1.8	6,908	55.2	5,392	43.1	4.0
Non-Hispanic Asian or Pacific Islander	177	1.7	5,434	50.5	5,139	47.8	3.4
Other or unknown	42	3.3	738	58.4	484	38.3	8.0
Diagnosis year							
1998-2000	1,456	2.4	34,949	56.8	25,081	40.8	5.5
2001-2003	3,513	3.9	53,377	58.5	34,379	37.6	9.3
Tumor size, cm							
< 1	890	3.0	20,721	69.2	8,310	27.8	9.7
1-1.9	1,715	2.8	41,167	67.2	18,360	30.0	8.6
2-4.9	1,875	3.6	24,924	47.4	25,730	49.0	6.8
5+	489	5.4	1,514	16.7	7,060	77.9	6.5
Tumor grade							
I or II	3,067	3.2	59,495	61.4	34,370	35.4	8.2
III	1,902	3.4	28,831	51.6	25,090	45.0	7.1
Cancer stage							
I	2,122	2.7	53,819	69.5	21,564	27.8	9.0
II	2,445	3.6	33,220	49.2	31,864	47.2	7.2
III	402	5.2	1,287	16.7	6,032	78.1	6.2
ER status							
Positive	3,367	3.2	62,658	59.9	38,633	36.9	8.0
Negative	985	3.5	15,177	53.7	12,095	42.8	7.6
Unknown or not done	617	3.1	10,491	52.9	8,732	44.0	6.6
Lymph node status							
Positive	2,059	3.9	23,243	44.1	27,341	52.0	7.0
Negative	2,910	2.9	65,083	65.0	32,119	32.1	8.3
Histology type							
Lobular	1,382	5.5	12,472	49.8	11,190	44.7	11.0
Nonlobular	3,587	2.8	75,854	59.4	48,270	37.8	6.9
Previous cancer diagnosis							
Yes	728	4.0	8,682	47.8	8,767	48.2	7.7
No	4,241	3.1	79,644	59.2	50,693	37.7	7.7

Abbreviations: CPM, contralateral prophylactic mastectomy; CPM-A, proportion of all surgically treated patients who underwent CPM, CPM/(CPM + BCS + unilateral mastectomy); CPM-M, proportion of all mastectomy patients who underwent CPM, CPM/(CPM + unilateral mastectomy); BCS, breast-conserving surgery; ER, estrogen receptor.
*The absolute values for the CPM-M column are the same as the CPM column.

DISCUSSION

In 1991, a National Cancer Institute Consensus Conference endorsed BCS or lumpectomy as the preferred treatment for early-stage breast cancer.[19] This recommendation was based on the results of prospective randomized trials showing that the survival rates were equal after BCS and mastectomy.[20-21] Yet, we found that the CPM rate doubled for all stages of breast cancer in the United States from 1998 through 2003. Importantly, these trends continued to the end of our 6-year study period with no plateau effect. These findings represent a dramatic change toward more aggressive breast cancer surgery in the United States. Still, the rate of BCS also increased during our study period. Thus, patients are increasingly choosing between minimal surgery (BCS) or more aggressive surgery (bilateral mastectomy) instead of unilateral mastectomy.

We identified certain clinical and pathologic factors that were associated with CPM rates. Young patient age, non-Hispanic white race, and lobular type histology were associated with significantly higher CPM-A and CPM-M rates. Polednak, [22] using data from the Connecticut Tumor Registry, also reported that young age and lobular histology were associated with higher CPM rates. We also found that CPM rates were significantly higher for patients with a previous

Table 2. Multivariate Analysis of Factors Associated With CPM

Factor	CPM-A *v* All Surgical Treatment				CPM-M *v* Unilateral Mastectomy			
	OR	95% CI	*P**	*df*	OR	95% CI	*P**	*df*
Age, years								
18-39	7.41	6.50 to 8.44	< .0001	4	7.96	6.96 to 9.09	< .0001	4
40-49	5.06	4.54 to 5.65			5.86	5.24 to 6.56		
50-59	3.21	2.88 to 3.58			3.97	3.55 to 4.43		
60-69	1.81	1.61 to 2.04			2.06	1.82 to 2.32		
70-79	1.00	Referent			1.00	Referent		
Race/ethnicity								
Non-Hispanic white	2.60	2.25 to 2.99	< .0001	1	2.65	2.29 to 3.06	< .0001	1
Hispanic	1.09	0.91 to 1.32			0.96	0.80 to 1.17		
Non-Hispanic black	1.00	Referent			1.00	Referent		
Non-Hispanic Asian or Pacific Islander	1.05	0.85 to 1.29			0.76	0.61 to 0.94		
Other or unknown	1.91	1.36 to 2.69			1.85	1.30 to 2.63		
Diagnosis year								
1998-2000	1.00	Referent	< 0.0001	1	1.00	Referent	< .0001	1
2001-2003	1.60	1.50 to 1.70			1.76	1.65 to 1.88		
Cancer stage								
I	1.00	Referent	.1081	2	1.00	Referent	.5694	2
II	1.09	0.98 to 1.23			0.94	0.83 to 1.06		
III	1.25	1.02 to 1.53			0.92	0.75 to 1.13		
Tumor size, cm								
< 1	0.81	0.68 to 0.95	< .0001	3	1.54	1.30 to 1.82	< .0001	3
1-1.9	0.69	0.59 to 0.81			1.39	1.19 to 1.62		
2-4.9	0.78	0.68 to 0.90			1.11	0.97 to 1.28		
5+	1.00	Referent			1.00	Referent		
Tumor grade								
I or II	1.02	0.95 to 1.09	.6609	1	1.11	1.03 to 1.19	.0035	1
III	1.00	Referent			1.00	Referent		
ER status								
Positive	1.00	Referent	.1677	2	1.00	Referent	.0370	2
Negative	1.08	0.99 to 1.17			1.05	0.97 to 1.14		
Unknown or not done	1.05	0.96 to 1.15			0.91	0.83 to 1.00		
Lymph node status								
Positive	1.00	Referent	.3829	1	1.00	Referent	.0001	1
Negative	0.96	0.87 to 1.05			1.21	1.10 to 1.33		
Histology type								
Nonlobular	1.00	Referent	< .0001	1	1.00	Referent	< .0001	1
Lobular	2.18	2.04 to 2.34			1.80	1.68 to 1.94		
Previous cancer diagnosis								
No	1.00	Referent	< .0001	1	1.00	Referent	.0091	1
Yes	1.64	1.51 to 1.78			1.12	1.03 to 1.22		

Abbreviations: OR, odds ratio; CPM, contralateral prophylactic mastectomy; CPM-A, proportion of all surgically treated patients who underwent CPM; CPM-M, proportion of all mastectomy patients who underwent CPM; ER, estrogen receptor.
*Controlling for registries.

history of other cancers. In our study, larger tumor size was associated with a higher CPM-A rate, but with a lower CPM-M rate. Favorable prognostic factors (smaller tumor size, negative lymph node status, and lower tumor grade) were associated with a significantly higher CPM-M rate; such patients are probably more likely to benefit from CPM because their survival time is longer and thus their subsequent risk of contralateral breast cancer is greater.

Other investigators have reported geographic variations in the surgical treatment of breast cancer.[23,24] Nattinger et al[24] reported that BCS rates were highest in the mid-Atlantic and New England regions and lowest in the south central regions. In our study, we found no general geographic trends (east coast *v* west coast *v* midwest *v* south) of CPM rates in the United States.

Previous studies have demonstrated the effectiveness of CPM in preventing contralateral breast cancer.[14-17] In a study of 745 breast cancer patients with a family history of breast cancer, McDonnell et al[15] reported that CPM reduced the incidence of contralateral breast cancer by more than 90%. However, the effectiveness of CPM in preventing breast cancer mortality is not as clear. A recent Cochrane review of eight studies included 1,708 patients who underwent CPM; the authors concluded that CPM decreased the incidence of contralateral breast cancer, but was not associated with any survival improvement.[25] Yet, in a retrospective cohort study of 1,072 patients from the Cancer Research Network, Herrinton et al[16] reported that CPM was associated with a significant decrease in the breast cancer mortality rate (CPM, 8.1%; no CPM, 11.7%). Peralta et al[14] demonstrated that CPM significantly increased the disease-free survival rate, but not the overall survival rate.

The potential benefit of CPM is greatest for patients who have the highest risk of contralateral breast cancer. Although absolute indications

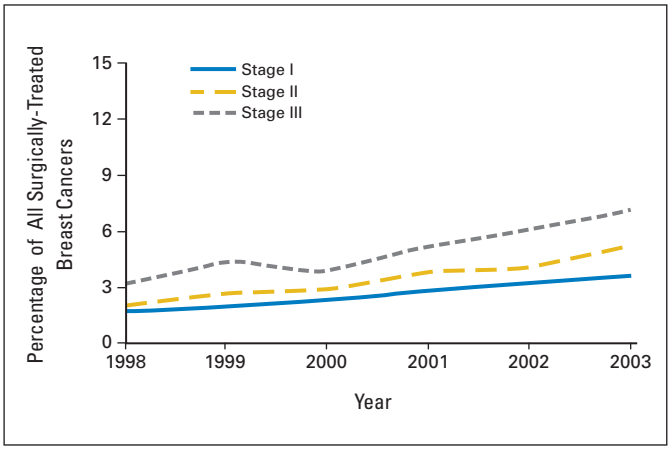

Fig 1. Trends in the proportion of all surgically treated patients who underwent contralateral prophylactic mastectomy (CPM-A) by cancer stage at diagnosis. The Cochran-Armitage tests for trend for CPM-A rates overall and by stage were significant ($P < .001$).

Table 3. CPM Rates by Geographic Location (registry)

Location	No. of CPMs	CPM-A*	CPM-M*
San Francisco-Oakland, CA	286	2.5%	6.4%
Connecticut	140	1.4%	4.6%
Metropolitan Detroit, MI	266	2.4%	5.4%
Hawaii	67	1.9%	4.8%
Iowa	424	5.6%	10.5%
New Mexico	164	4.2%	9.7%
Seattle (Puget Sound), WA	443	3.7%	9.2%
Utah	72	1.8%	3.7%
Metropolitan Atlanta, GA	372	5.6%	13.5%
San Jose-Monterey, CA	158	2.8%	6.4%
Los Angeles	499	2.5%	6.4%
Greater California†‡	1216	4.2%	9.5%
Kentucky‡	194	3.1%	5.9%
Louisiana‡	207	3.2%	5.8%
New Jersey‡	453	3.2%	8.5%

NOTE. Excludes the Rural Georgia registry because of small numbers.
Abbreviations: CPM, contralateral prophylactic mastectomy; CPM-A, proportion of all surgically treated patients who underwent CPM; CPM-M, proportion of all mastectomy patients who underwent CPM.
*$P < .0001$ for χ^2 test with 14 degrees of freedom.
†Includes all areas of California, except for San Francisco-Oakland, Los Angeles, and San Jose-Monterey.
‡Data only available for patients diagnosed in 2000 through 2003.

for CPM are not established, the Society of Surgical Oncology has published criteria that physicians should consider for mastectomy of the contralateral, intact breast.[26] The decision to undergo CPM is complex, and many factors likely contribute to its increased frequency. In a review of the National Prophylactic Mastectomy Registry, Montgomery et al[27] reported that the most common reason for CPM was physicians' advice regarding risk of contralateral breast cancer.

Patient satisfaction and psychological and social outcomes after CPM have been examined by several investigators.[27-29] Frost et al[28] reported that 83% of patients were either satisfied or very satisfied with their decision to undergo CPM at a mean of 10 years after surgery. Montgomery et al[27] reported that the most common reasons for regret after CPM were a poor cosmetic outcome and diminished sense of sexuality. Geiger et al[29] found that patients who underwent CPM were less likely to express breast cancer concern compared with patients who did not undergo CPM.

Nevertheless, patients with unilateral breast cancer have options that are less extreme than CPM. Surveillance with clinical breast examination, mammography, and newer imaging modalities such as breast magnetic resonance imaging may detect cancers at earlier stages.[30-32] Tamoxifen, given as adjuvant therapy for ER-positive breast cancer, significantly reduces the rate of contralateral breast cancer.[33-35] Aromatase inhibitors may reduce the risk of contralateral breast cancer as much as, or even more than, tamoxifen.[36] Because hormone therapy reduces the risk of contralateral breast cancer for patients with ER-positive breast cancer, we anticipated that CPM rates would be lower for such patients; however, our data did not show this expected finding. Ovarian ablation and cytotoxic chemotherapy also reduce the risk of contralateral breast cancer.[37,38]

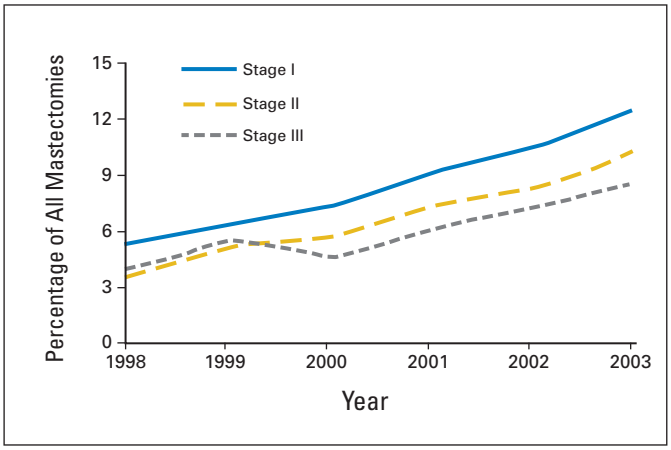

Fig 2. Trends in the proportion of all mastectomy patients who underwent contralateral prophylactic mastectomy (CPM-M) by cancer stage at diagnosis. The Cochran-Armitage tests for trend for CPM-M rates overall and by stage were significant ($P < .001$).

Because our study used cancer registry data, detailed patient and tumor information that may have influenced treatment decisions were not available. Important factors regarding family history, genetic testing results, reconstructive surgery, tamoxifen use, systemic chemotherapy, and mammographic findings were not available to us. Moreover, our study did not include patients who later chose CPM years after initial treatment, potentially underestimating the true CPM rate. Likewise, our study excluded patients with two breast cancer diagnoses in the same month, even when one was coded as including a CPM. Polednak found that a small proportion of these cases resulted in a cancer diagnosis in the apparently uninvolved breast; therefore, we removed these cases again leading to an underestimation of the true CPM rate.[22] Our use of SEER data is supported by a detailed review that confirmed cases coded by one SEER registry as undergoing a CPM did involve a bilateral mastectomy where only one breast was considered to have cancer.[39]

Despite the potential limitations of our study, SEER is population-based and includes patients from diverse locations and practices in the United States, making our findings broadly reflective of standard practice. Ironically, our population-based study demonstrated that although the BCS rate increased in the United States from 1998 to 2003, the bilateral mastectomy rate also increased while the unilateral mastectomy rate decreased. We found that the CPM-A rate

was greater for patients with more advanced stage cancer (because these patients frequently require mastectomy), but the CPM-M rate was greater for patients with earlier stage cancer. These observations are consistent with a study by Nekhlyudov et al,[40] which found that 29% of women undergoing CPM had regional disease. Future prospective studies are critically needed to evaluate the decision-making processes leading to CPM.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Acknowledgment

We acknowledge Mary Knatterud, PhD, Department of Surgery, University of Minnesota, Minneapolis, MN, for her editorial assistance.

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).