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EPIDEMIOLOGY

The use of contralateral prophylactic mastectomy among elderly patients in the United States

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Abstract

Purpose Previous studies have reported increased rates of contralateral prophylactic mastectomy (CPM) in the United States among women with unilateral breast cancer. These trends have primarily focused on younger breast cancer patients. Given the growing aging population in the United States, we sought to determine whether CPM use is also increasing in elderly patients.

Methods This population-based study identified patients in the surveillance epidemiology and end results (SEER) data. We determined the rate of CPM as a proportion of all surgically treated patients and as a proportion of all mastectomies. We compared the unadjusted CPM rates over the study period using the Cochrane-Armitage test for trend. We used a logistic regression model to test for the factors associated with CPM utilization.

Results We identified 261,281 patients ≥ 65 years who underwent surgical treatment for breast cancer. For all patients treated with surgery for invasive breast cancer, the use of CPM increased from 1 in 2004 to 3% in 2014 (200% increase). Among mastectomy patients, the use of CPM increased from 3 in 2004 to 7% in 2014 (133% increase). Young age, non-Hispanic white race, lobular histology, higher grade, increased stage, negative lymph node status, and recent year of diagnosis were significantly associated with increased CPM rates.

Conclusions For elderly patients the use of CPM has continued to increase in the United States. These observations warrant concern in light of increasing evidence that CPM does not improve oncological outcomes and is associated with increased morbidity in older patients.

Keywords Contralateral prophylactic mastectomy · SEER · Trends over time

Introduction

The National Cancer Institute's Surveillance Epidemiology and End Results (SEER) tumor registry began coding the use of contralateral prophylactic mastectomy (CPM) in 1998. At that time, the proportion of patients who underwent CPM in the United States was quite low (1–2%). However, a study published in 2007 using the SEER registry reported that CPM rates increased by 150% between 1998 and 2003 [1]. In this analysis, the CPM rates were still increasing at the end of the study period with no apparent plateau. Interestingly, no practice-changing studies suggesting a benefit from CPM were reported during that 6-year period. Subsequently, other population-based studies and multiple single-center studies have confirmed these trends [2–5].

Over the past decade, numerous investigations have evaluated important outcomes after CPM including complications, costs, patient satisfaction, and survival [2–11]. In addition, multiple editorials have been written in clinical journals and in the popular press discussing the increased use of CPM [12, 13]. Since 2007, clinical guidelines from the United States and Europe have been published that outline specific indications for risk-reducing surgery including CPM [6, 7]. The American Society of Breast Surgeons has recommended against the use of CPM for average risk women with unilateral breast cancer [14].

Most of the research surrounding trends and outcomes of CPM have focused on younger women with breast cancer. However, given the aging population in the United States, we sought to determine the use of CPM in women 65 years

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and older, and to evaluate factors associated with its use. Understanding the use of CPM in this population of patients is important because elderly patients are more likely to experience complications, less likely to harbor deleterious genetic mutations, and more likely to have other competing causes of mortality [15, 16].

Methods

We used the SEER program database to examine rates and trends of CPM use in women aged 65 years and older diagnosed with unilateral breast cancer from 2004 to 2014. 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. CPM was defined using the SEER mastectomy surgery codes that included "with removal of uninvolved contralateral breast." In order to capture the breadth of surgical options, we determined the overall rate of CPM-all (CPM-A; i.e., proportion of all surgically treated patients who underwent CPM) and the rate of CPM-mastectomy (CPM-M; i.e., proportion of all mastectomy patients who underwent CPM) which excluded patients treated with breast-conserving surgery (BCS), since these patients generally do not undergo CPM. We limited our study to female patients aged 65 years and older diagnosed with unilateral invasive breast cancer or ductal carcinoma in situ (DCIS) from 2004 to 2014. We excluded women with bilateral disease, disease of unknown laterality, those without microscopic confirmation of cancer, those without data on tumor size or tumor grade and patients with stage IV disease. Patients diagnosed with grade IV (undifferentiated, anaplastic) breast cancer were also excluded as this is not commonly reported and may represent non-breast malignancies that have metastasized to the breast. We excluded women with multiple primary breast cancers diagnosed within the same month to ensure that the contralateral mastectomy was prophylactic. In addition, we excluded women who underwent radical or extended radical mastectomy. Patients with no recorded treatment or those diagnosed at autopsy, on death certificate, at nursing homes only or in registries with less than 30 CPM cases (Alaska) were also excluded.

We compared demographic and tumor variables for patients who underwent CPM, BCS, or unilateral mastectomy for each year of our study period (2004 through 2014). We compared the unadjusted CPM rates over the study period using the Cochrane-Armitage test for trend. We used a logistic regression model to test for the factors associated with CPM utilization and to model the use of CPM-A (the proportion of all surgically treated patients who underwent CPM). All models included the patients' age, race, year of diagnosis, previous history of non-breast cancer diagnosis, cancer stage, tumor size (<2.0 cm, 2.0 to 4.9 cm, or ≥ 5.0 cm), tumor grade (I and II and III), estrogen receptor (ER) status (positive, negative, or unknown), lymph node status (positive, negative, or unknown), 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 study period. In all models, we performed sensitivity analyses to ensure that the observed effects were not a product of coding classifications and modeling decisions. All statistical analysis was completed using SAS software, version 9.3 (SAS Institute, Cary, NC). Our study was exempt from review by the Human Subjects Committee of the University of Minnesota's institutional review board because it used a pre-existing de-identified data source.

Results

We identified 261,281 patients with surgically treated stage 0–III breast cancer during our study period (Table 1). Most women underwent either BCS (63%) or unilateral mastectomy (35%), and 2% underwent CPM (CPM-A in Table 1). Of those who underwent a mastectomy, 5% underwent CPM (CPM-M in Table 1). Patient and tumor characteristics for each group are presented in Table 1.

We observed an increase in CPM rates for all ages, stages and within all geographic registries (Fig. 1a, b). The overall trend of increasing CPM rates continued to the end of our study period with a potential plateau beginning in 2013 (Fig. 1a). Beginning in 2013, there was a decreasing CPM rate in 70–74-year-old women as well as in women with stage I breast cancers. However, other ages and stages continued to increase significantly ($p<0.05$). We observed similar significant increases ($p<0.05$) when we stratified patients by cancer stage (Fig. 1c), age (Fig. 1d), and geographic registry (Table 2).

We evaluated the trends for specific subgroups to identify possible attenuation in the CPM rates. The overall CPM rates for stage I (2012, 2.1%; 2014, 2.5%) and stage II (2012, 2.7%; 2014, 3.2%) breast cancer patients continued to increase during the last 3 years of our study (Fig. 1c). When stratified by age, we observed significant increases across all age groups with the most prominent and significant overall increase in women 65–69 years old (2004, 2.6%; 2014, 9.8%).

We observed considerable geographic variation in CPM-A rates (Table 2). During the early period (2004–2009), the CPM-A rate was lowest in the Utah registry (0.3%) and highest in rural Georgia (2.9%). In the later period (2010–2014), the CPM-A rate was lowest in the Detroit (metropolitan) registry (1.2%) and

Table 1 Patient characteristics 2004–2014 (total number of patients: 261,281)

	CPM-A		BCS		Unilateral mastectomy		CPM-M
	n	%	*n*	%	*n*	%	%
No. of patients	4557	2	164,068	63	92,656	35	5
Age, years							
65–69	1952	2.4	51,843	64.1	27,065	33.5	7
70–74	1315	2.0	41,175	63.8	22,009	34.1	6
75–79	758	1.4	32,790	62.3	19,115	36.3	4
80+	532	0.8	38,260	60.5	24,467	38.7	2
Race							
Non-Hispanic White	4044	1.8	140,950	63.7	76,318	34.5	5
Black	262	1.2	12,889	58.8	8763	40.0	3
Asian	217	1.3	9007	55.7	6933	42.9	3
Other	34	1.8	1222	64.4	642	33.8	5
Diagnosis year							
2004–2009	1489	1.1	81,186	61.5	49,236	37.3	3
2010–2014	3068	2.4	82,882	64.1	43,420	33.6	7
Tumor size (cm)							
< 2	2557	1.6	114,515	72.1	41,830	26.3	6
2–4.9	1380	1.9	35,584	49.3	35,169	48.8	4
≥ 5	320	2.3	3302	23.7	10,330	74.0	3
Missing	300	1.8	10,667	65.5	5327	32.7	5
Tumor grade							
I or II	3053	1.7	117,403	65.6	58,483	32.7	5
III	1238	1.9	36,783	55.3	28,473	42.8	4
Missing	266	1.7	9882	62.4	5700	36.0	4
Cancer stage							
DCIS	836	1.9	31,960	73.1	10,945	25.0	7
I	2079	1.7	90,006	71.9	33,137	26.5	6
II	1318	1.9	34,299	50.6	32,101	47.4	4
III	246	1.3	4506	23.8	14,153	74.9	2
Missing	78	1.4	3297	57.9	2320	40.7	3
Estrogen receptor status							
Positive	3615	1.7	135,875	64.5	71,238	33.8	5
Negative	660	2.0	17,837	53.5	14,856	44.5	4
Unknown or not done	282	1.6	10,356	60.2	6562	38.2	4
Lymph node status							
Positive	3199	2.1	98,700	63.4	53,668	34.5	6
Negative	657	1.3	19,627	40.2	28,598	58.5	2
Unknown	701	1.2	45,741	80.5	10,390	18.3	6
Histology type							
Nonlobular	3912	1.6	152,280	64.0	81,562	34.3	5
Lobular	645	2.7	11,788	50.1	11,094	47.2	5
Previous cancer diagnosis							
No	2069	2.3	56,336	61.5	33,165	36.2	6
Yes	2488	1.5	107,732	63.5	59,491	35.1	4

highest in the rural Georgia registry (4.8%). When we stratified our registries by year category, we observed a significant increase in CPM-A rates in all registries over time (Table 2). We did not observe any obvious trends in

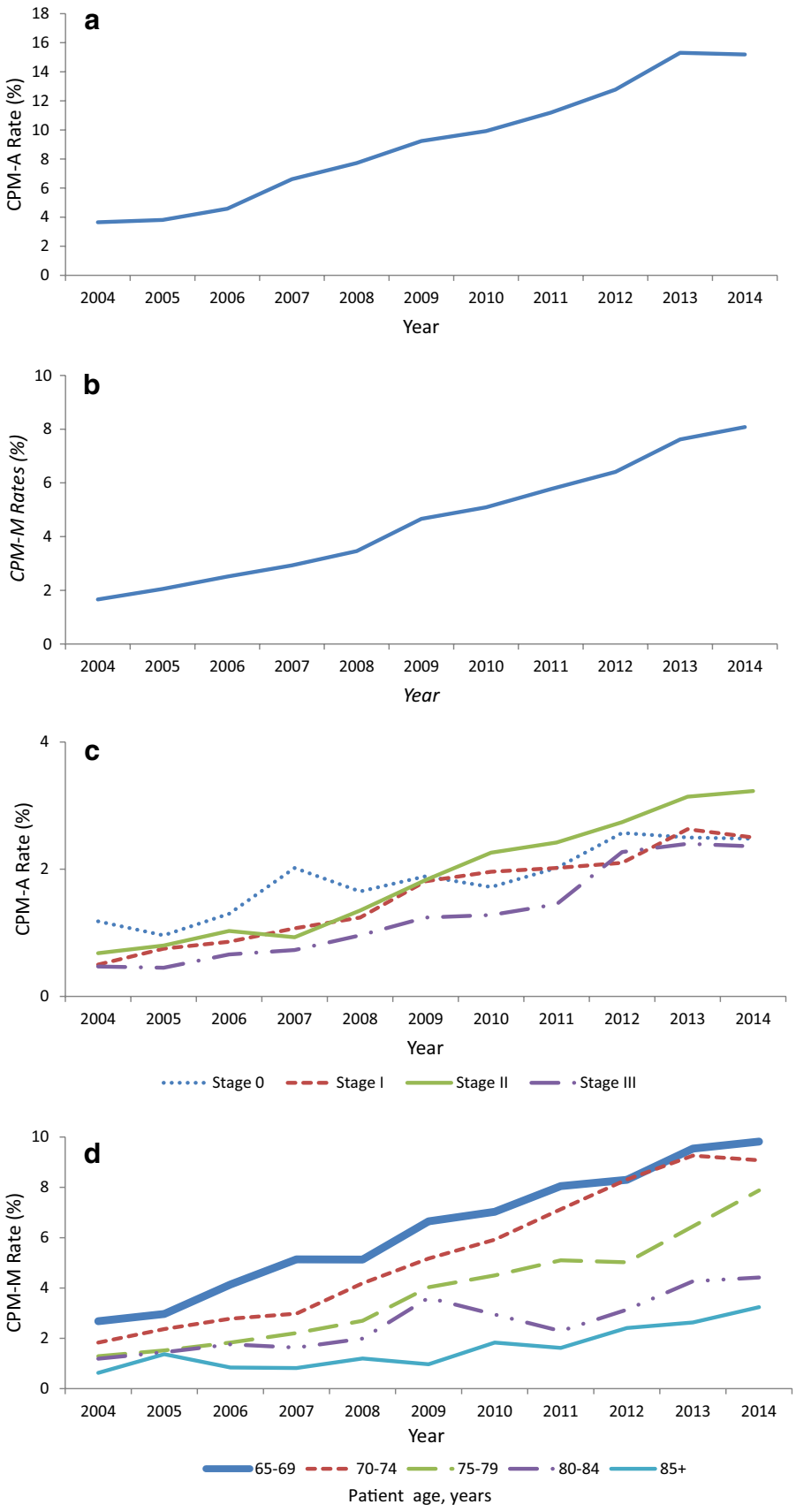

Fig. 1 **a** Temporal trends in the proportion of all surgically treated patients, aged ≥ 65, who underwent contralateral prophylactic mastectomy (CPM-A). **b** Temporal trends in the proportion of mastectomy patients, aged ≥ 65, who underwent contralateral prophylactic mastectomy (CPM-M). **c** Temporal trends in the proportion of all surgically treated patients, aged ≥ 65, who underwent contralateral prophylactic mastectomy (CPM-A), by cancer stage. **d** Temporal trends in the proportion of mastectomy patients, aged ≥ 65, who underwent contralateral prophylactic mastectomy (CPM-M) by patient age groups

Table 2 Rates of contralateral prophylactic mastectomy among all surgically treated patients by geographic location (registry) and year

2004–2009 (%)	2010–2014 (%)	
Location		
Atlanta (Metropolitan)	1.4	2.4
California	1.4	2.8
Connecticut	0.7	2.0
Detroit (Metropolitan)	0.4	1.2
Greater Georgia	1.5	2.8
Hawaii	1.2	1.7
Iowa	1.7	3.0
Kentucky	1.1	3.1
Los Angeles	0.9	2.3
Louisiana	1.1	2.5
New Jersey	0.7	1.4
New Mexico	1.3	2.2
Rural Georgia	2.9	4.8
San Francisco-Oakland	1.0	1.8
San Jose-Monterey	0.8	1.6
Seattle (puget sound)	1.9	3.4
Utah	0.3	2.7

CPM rates based on specific geographic locations in the United States.

Factors associated with CPM

Multivariate logistic regression analysis (Table 3) demonstrated that non-Hispanic white race, previous cancer diagnosis, lobular histology, higher grade, higher stage, estrogen-receptor negative status, negative lymph node status, and larger tumor size were also significantly associated with increased CPM-A rates ($p \leq 0.05$). Patients who were older were significantly less likely to receive a CPM, as well as black and other race. Cancer stage (Stage II versus Stage 0), lymph node status (negative versus positive) and non-lobular histology were also significantly less likely to receive a CPM. After controlling for all other factors, the use of CPM-A (OR 2.02; 95% CI 1.89–2.16) and CPM-M (OR 2.17; 95% CI 2.02–2.33) markedly increased in the later time period (2010-2014) as compared to the earlier 2004–2009 time period (Table 4).

Table 3 Multivariable analysis of factors associated with receipt of contralateral prophylactic mastectomy among all surgically treated patients (CPM-A)

	OR	95% CI	
Age, years			
65–69	Referent		
70–74	**0.85**	**0.78**	**0.91**
75–79	**0.58**	**0.53**	**0.64**
≥ 80	**0.34**	**0.30**	**0.38**
Race			
Non-Hispanic White	Referent		
Black	**0.64**	**0.56**	**0.74**
Other	**0.74**	**0.64**	**0.86**
Diagnosis year			
2004–2009	Referent		
2010–2014	**2.02**	**1.89**	**2.16**
Tumor grade			
I or II	Referent		
III	1.06	0.98	1.15
Cancer stage			
0	**0.83**	**0.74**	**0.94**
I	Referent		
II	**1.24**	**1.09**	**1.40**
III	0.93	0.75	1.15
Estrogen receptor status			
Positive	Referent		
Negative	**0.85**	**0.77**	**0.93**
Unknown or not done	1.02	0.85	1.21
Lymph node status			
Positive	Referent		
Negative	**0.60**	**0.53**	**0.67**
Unknown	**0.64**	**0.57**	**0.71**
Histology status			
Lobular	Referent		
Nonlobular	**0.61**	**0.55**	**0.67**
Previous cancer diagnosis			
No	Referent		
Yes	**1.99**	**1.85**	**2.14**

Bold values indicate $p < .05$

Discussion

In our study, we found that although rates of CPM were generally low among elderly women with breast cancer, the use of CPM increased from 3% in 2004 to 7% in 2014 (133% increase). Increasing rates of CPM utilization were demonstrated across all cancer stages, all age groups, and in all geographic registries. These findings confirm the dramatic change toward more aggressive breast cancer surgery in the United States for elderly women. Surprisingly, these trends have continued despite increasing evidence that CPM provides no survival advantage [8, 9] and is associated with increased costs [10], and higher complication rates [12]. Upon examining specific subgroups of patients, we found that the increased use of CPM may be leveling off for some specific subgroups, such as for stage III breast cancer. In addition, we found that the overall CPM rate for 70–74-year-old women decreased slightly beginning in 2013.

Table 4 Multivariable analysis of factors associated with receipt of contralateral prophylactic mastectomy among all mastectomy patients (CPM-M)

	OR	95% CI	
Age, years			
65–69	Referent		
70–74	**0.85**	**0.78**	**0.92**
75–79	**0.57**	**0.52**	**0.62**
≥ 80	**0.31**	**0.28**	**0.34**
Race			
Non-Hispanic White	Referent		
Black	**0.59**	**0.51**	**0.68**
Other	**0.52**	**0.44**	**0.60**
Diagnosis year			
2004–2009	Referent		
2010–2014	**2.17**	**2.02**	**2.33**
Tumor grade			
I or II	Referent		
III	0.99	0.91	1.07
Cancer stage			
0	**1.16**	**1.03**	**1.30**
I	Referent		
II	1.05	0.93	1.20
III	**0.62**	**0.50**	**0.77**
Estrogen receptor status			
Positive	Referent		
Negative	0.98	0.89	1.09
Unknown or not done	0.86	0.72	1.03
Lymph node status			
Positive	Referent		
Negative	**0.52**	**0.46**	**0.58**
Unknown	**1.25**	**1.13**	**1.38**
Histology status			
Lobular	Referent		
Nonlobular	**0.74**	**0.67**	**0.82**
Previous cancer diagnosis			
No	Referent		
Yes	**1.13**	**1.05**	**1.22**

Bold values indicate $p < .05$

One of the main reasons cited by patients for the decision to undergo CPM is to prevent the occurrence of contralateral breast cancer [14, 15]. Although the absolute risk of developing a contralateral breast cancer is greater than the general population, in patients without a genetic mutation it is still less than 1% per year [16–19]. The Early Breast Cancer Trialists' Collaborative Group reported that the annual rate of contralateral breast cancer was about 0.4 to 0.5% [16]. Similar rates were also found in a single-center retrospective study in Buenos Aires of 3864 patients surgically treated for breast cancer, the risk of a contralateral breast carcinoma was 0.9% per year, with a 15-year accumulated risk of 12.75% [20]. Furthermore, the rates of metachronous contralateral breast cancer in the United States have significantly declined in recent decades, likely secondary to the increased use of systemic adjuvant therapy [21]. In the recently published TAILORx study, the 9-year cumulative risk of contralateral breast cancer was only 1.4% [22]. Systemic adjuvant chemotherapy is estimated to reduce the risk by 20%, tamoxifen by 50% and aromatase inhibitors by about 60% [23, 24].

While the oncologic benefits of CPM are questionable in the general population, the utility of CPM in elderly may be even more uncertain as previous studies have shown that older patients have a better prognosis compared to younger patients, with more favorable breast cancer subtypes [25–28]. Furthermore, the incidence of deleterious mutations is lower among elderly patients with newly diagnosed breast cancer; thus, the risk of metachronous contralateral breast cancer is even further diminished [29]. Additionally, elderly women are more likely to have estrogen receptor positive-breast cancer that will be treated with endocrine therapy; since endocrine therapy substantially reduces the risk of contralateral breast cancer, the oncologic benefit of a CPM is thus even further diminished for elderly patients [30]. In addition to decreased potential benefits of CPM, older patients are more likely to experience complications after bilateral mastectomy [31]. Finally, elderly patients are more likely to have other competing mortality risks (e.g. cardiovascular), thus further limiting the oncologic benefits of CPM for elderly patients.

In general, the reasons for the continued increase of CPM, despite decreasing risk of contralateral breast cancer, remain unclear but are likely multifactorial. Improved techniques and outcomes with mastectomy and reconstruction may in part contribute to these trends. In a previous analysis of the SEER database, Agarwal et al. reported that implant-based reconstruction was significantly associated with receipt of CPM [32]. Additionally, the rising use of preoperative breast MRI in the United States has been associated with rising CPM rates [15, 19]. Finally, increased germ line mutation testing may also contribute to increasing CPM rates as testing has been shown to be significantly associated with CPM, even among patients who test negative for BRCA mutations [33]. In one single-center study, the CPM rate was 40% even among patients who tested negative for mutations [20].

Since the original SEER study documenting an increase in CPM use from 1998 to 2003, a number of guidelines for risk-reducing surgery including bilateral mastectomy and CPM have been published [1]. A consensus statement from the American Society of Breast Surgeons (ASBS) recommends consideration of CPM only among women who are at a significant risk for contralateral breast cancer; specifically women who are BRCA1/2 carriers, with a strong family

history of history of chest radiation prior to age 30 [34]. Furthermore, they advise a discussion with every patient (excluding high risk patients) considering CPM that incorporates the low likelihood of developing a contralateral breast cancer, the higher risk of complications, the risk of complications delaying necessary adjuvant oncologic treatment, and that the CPM will not reduce the recurrence risk of the index cancer, nor influence the need for other adjuvant therapies [35–40]. The National Comprehensive Cancer Network (NCCN) guidelines mirror those of ASBS only recommending consideration of CPM in patients of high risk and discouraging CPM in others [6].

However, despite these recommendations, CPM use continues to increase, even in the elderly. Most CPMs are performed on patients who do not have guideline-recommended clinical indications for the procedure. In a longitudinal survey study of 2290 women, Hawley et al. reported that 68.9% of patients who underwent CPM had no major genetic or familial risk factors for contralateral breast cancer [21]. Many women substantially overestimate their risk of contralateral breast cancer at the time of diagnosis [41] possibly influencing their decision to undergo a CPM. In a prospective survey study of women with unilateral breast cancer, Abbott et al. reported that patients markedly overestimated their 10-year cumulative risk of contralateral breast cancer [41]. Finally, many women have unrealistic expectations of oncologic benefits of CPM. In a survey study of young women who underwent CPM, Rosenberg et al. reported that 94% of women cited "desire to improve my survival/extend my life" as an extremely or very important reason for CPM [42]. Similarly, 85% of women cited "desire to prevent breast cancer from spreading to other places in my body" as another reason for CPM [24]. In addition, CPM rates continue to increase in the setting of patient misperceptions regarding contralateral breast cancer risk and oncologic outcomes of CPM.

Limitations

Our study has several limitations to consider. First, SEER does not collect data on many factors that may have influenced treatment decisions for patients with unilateral breast cancer. For example, family history, co-morbidities, use of genetic testing, results of genetic testing, receipt of chemotherapy and endocrine therapy, and use of MRI are not collected, and cannot be analyzed to understand treatment choices. Additionally, hospital and surgeon characteristics are not collected by SEER which may impact treatment decisions. Further, this study may underestimate the true CPM rate, as SEER only codes the initial treatment; therefore, patients who chose CPM more than 6 months after initial surgery would not be included in this analysis. Finally, this analysis excludes any patient who has DCIS or invasive breast cancer bilaterally. Thus, women who underwent CPM and were later found to have occult DCIS or invasive breast cancer in the CPM specimen would be excluded from this analysis. Despite these limitations, our observations are robust and represent clinical practice across the United States.

Conclusions

In summary, we found that the overall CPM rates are increasing in the United States for women ≥ 65 years old. These findings are troublesome because previous studies have indicated that most patients who undergo CPM lack clinical indications for the procedure and the patients may have misconceptions regarding their cancer risk and role of CPM. Additionally, older patients are even less likely to benefit from CPM and more likely to be harmed compared to younger patients, making increased rates in this population particularly concerning. Additional studies are still needed to understand the potential factors that contribute to the increased use of this aggressive surgical treatment for the management of breast cancer in this age group. Furthermore, physicians must identify and correct any misconceptions that their patients may have when diagnosed with breast cancer and making associated treatment decisions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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