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Survival Outcomes After Contralateral Prophylactic Mastectomy: A Decision Analysis

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Background	Contralateral prophylactic mastectomy (CPM) rates have substantially increased in recent years and may reflect an exaggerated perceived benefit from the procedure. The objective of this study was to evaluate the magnitude of the survival benefit of CPM for women with unilateral breast cancer.
Methods	We developed a Markov model to simulate survival outcomes after CPM and no CPM among women with stage I or II breast cancer without a BRCA mutation. Probabilities for developing contralateral breast cancer (CBC), dying from CBC, dying from primary breast cancer, and age-specific mortality rates were estimated from published studies. We estimated life expectancy (LE) gain, 20-year overall survival, and disease-free survival with each intervention strategy among cohorts of women defined by age, estrogen receptor (ER) status, and stage of cancer.
Results	Predicted LE gain from CPM ranged from 0.13 to 0.59 years for women with stage I breast cancer and 0.08 to 0.29 years for those with stage II breast cancer. Absolute 20-year survival differences ranged from 0.56% to 0.94% for women with stage I breast cancer and 0.36% to 0.61% for women with stage II breast cancer. CPM was more beneficial among younger women, stage I, and ER-negative breast cancer. Sensitivity analyses yielded a maximum 20-year survival difference with CPM of only 1.45%.
Conclusions	The absolute 20-year survival benefit from CPM was less than 1% among all age, ER status, and cancer stage groups. Estimates of LE gains and survival differences derived from decision models may provide more realistic expectations of CPM.

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The use of contralateral prophylactic mastectomy (CPM) among women with unilateral breast cancer has markedly increased in the United States during the past decade (1–5). These trends have been observed in retrospective single-center studies (1,3), national population databases (4,5), and state cancer registries (2). Similar trends have not been observed in Europe (6,7). Breast cancer patients report that the main reason they choose CPM is worry about the risk of contralateral breast cancer (CBC) (8), yet they tend to substantially overestimate their risk of developing CBC (9). CPM reduces the risk of CBC by approximately 90% (10–14), but the overall survival benefit is unclear (15–17).

Long-term survival in women with unilateral breast cancer treated with or without CPM depends upon several factors, including mortality of the primary breast cancer, risk of CBC, stage and mortality of the CBC, and the individual patient's overall life expectancy (LE). Prospective randomized trials comparing CPM with no CPM are not feasible. Retrospective studies evaluating a potential survival benefit with CPM are limited by short follow-up, potential selection bias, and lack of important clinical information (15,16,18).

The primary objective of this study was to assess the magnitude of the survival benefit of CPM among women with unilateral breast cancer using a simulated decision-analytic Markov model. Our aim was to provide projected long-term survival information by using a simulated Markov model for physicians and their patients when discussing breast cancer risk-reduction strategies.

Methods

Model Design

A Markov model (19) is a recursive decision tree that guides a hypothetical cohort between mutually exclusive health states depending on transition probabilities obtained from published data. We developed a Markov state-transition model to simulate survival outcomes after CPM and no CPM for women with stage I and II breast cancer without BRCA mutations (Figure 1). The model simulates the long-term prognosis of hypothetical cohorts of women with newly diagnosed unilateral breast cancer under two scenarios: 1) CPM (ie, double mastectomy) and 2) no CPM (assuming that women undergo either lumpectomy with radiation therapy

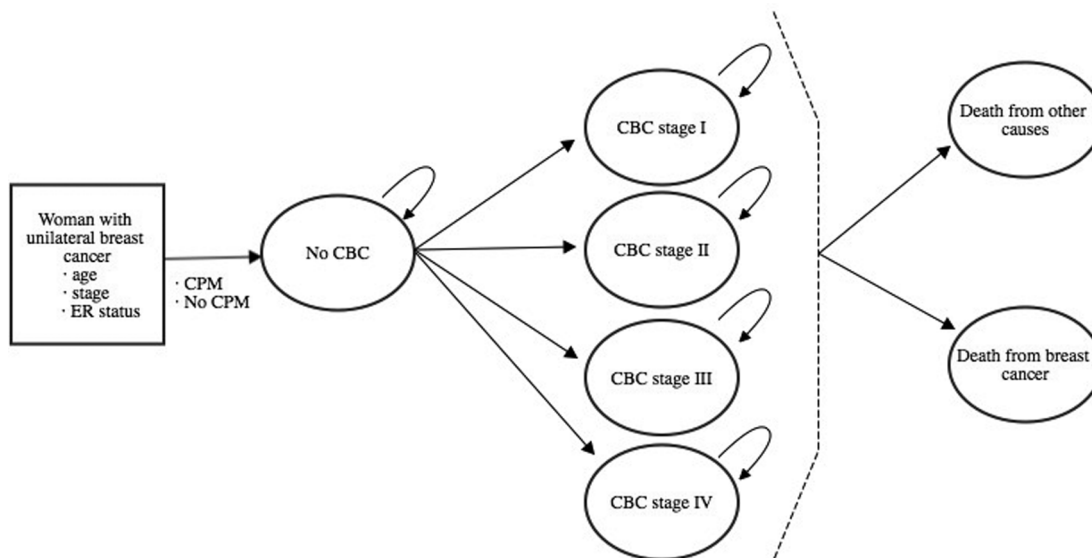


Figure 1. Markov model. Women in each Markov state (no contralateral breast cancer [CBC], CBC stage I, CBC stage II, CBC stage III, CBC stage IV) can die from other causes or die from breast cancer. Each cycle of the Markov model is 1 year. The model ran the lifetime of the cohort. For example, the model predicting life expectancy in the 40-year-old

or unilateral mastectomy). We projected the benefit of CPM for cohorts of women defined by age at breast cancer diagnosis (40, 50, or 60 years), stage of primary breast cancer (I, II), and estrogen receptor (ER) status (positive, negative).

The model tracks each cohort of women through health states over time. Each year after treatment of the ipsilateral cancer, women may die from their primary breast cancer, develop CBC, or experience no adverse event. After development of CBC, women are at an increased risk of dying from breast cancer (ie, the risk associated with their ipsilateral and contralateral cancers). Data from the 2008 life tables for US women were used to incorporate the age-specific annual risk of dying from other causes (20). Model output for each strategy consisted of LE, overall survival, and disease-free survival. The model was programmed using TreeAge Pro 2012 (TreeAge Software, Williamstown, MA).

Data Sources

The probabilities used in baseline analyses and the ranges evaluated in sensitivity analyses are listed in Table 1.

Cancer Incidence and Prognosis

Primary Breast Cancer. We derived stage-specific breast cancer mortality rates from the relative survival curves reported in the Surveillance, Epidemiology, and End Results (SEER) data (21). We used SEER stat (22) to obtain 20-year relative survival curves for patients with stage I or II breast cancer, where stage was defined by the American Joint Committee on Cancer SEER modified staging system. SEER reports a breast cancer–specific mortality risk (ie, $1 - \text{relative survival percentage}$) for women with stage I breast cancer of 1.8% at 10 years and 10.0% at 20 years. For women with stage II breast cancer, cancer-specific mortality was 23.1% at 10 years and 42.2% at 20 years (22).

Contralateral Breast Cancer. We assumed the stage-specific mortality associated with CBC was the same as reported by SEER.

cohort ran 61 cycles to obtain data through age 100 (lifetime). The model predicting life expectancy for the 50-year-old cohort ran 51 cycles, and the model for the 60-year-old cohort ran 41 cycles. To generate 20-year survival curves we only used model output for the first 20 years. CPM = contralateral prophylactic mastectomy; ER = estrogen receptor.

For patients who developed CBC, we added the stage-specific cancer mortality rate of their ipsilateral cancer to the stage-specific cancer mortality rate of their contralateral cancer.

Several studies have evaluated the risk of developing CBC (23–26). For our base-case values, we used the recent meta-analysis from the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) that reported an annual probability of invasive CBC of approximately 0.4% for patients with ER-positive breast cancer treated with tamoxifen and approximately 0.5% for patients with ER-negative breast cancer. All age, tumor, and treatment subgroups had probabilities less than 0.7% per year (26). We assumed that every woman in our cohort with ER-positive breast cancer was treated with endocrine therapy for our base-case analysis. Therefore, in our model at baseline we used an annual probability of developing CBC of 0.4% in ER-positive patients and 0.5% in ER-negative patients, varying from 0.2% to 0.7% in our sensitivity analysis to capture uncertainty and differences to treatment adherence to endocrine therapy.

CBC Stage. Using the Oregon State Cancer Registry database, Quan et al. (27) reported that more than 90% of CBCs were either ductal carcinoma in situ or early-stage breast cancer. To capture the maximum potential benefit of CPM, we modeled invasive breast cancer only as this would impact survival and used CBC probabilities reported by Quan et al. (27) after excluding ductal carcinoma in situ. We estimated that the probability of developing stage I CBC was 67%, the probability of developing stage II CBC was 24%, the probability of developing stage III CBC was 5%, and the probability of developing stage IV CBC was 4%. We used the stage distribution reported by SEER for primary breast cancer presentation in a sensitivity analysis (Table 1) (22).

Effectiveness of Contralateral Prophylactic Mastectomy. Several studies have demonstrated that CPM is effective in reducing the

risk of CBC (relative risk reduction: 83% to 97%) (10–14). We assumed that CPM reduced the annual risk of CBC by 90% in our base-case analysis. Because breast cancer surgery is associated with a very small risk of mortality (28,29), we did not incorporate surgical mortality into our model.

We assumed that the survival rates were the same after mastectomy as compared with lumpectomy and radiation for treatment of the affected breast (30). Thus, all of the survival benefit of bilateral mastectomies (ie, CPM) is obtained from removing the unaffected contralateral breast.

Sensitivity Analysis

We performed sensitivity analyses to assess the stability of results to variation in the base-case parameter estimates. The variables analyzed in the sensitivity analysis included probability of CBC, stage of CBC, and effectiveness of CPM. When several published point estimates were available for a particular parameter, we evaluated the full range of published estimates. In instances in which there were limited available published data and uncertainty for a variable estimate (eg, stage

of CBC), we varied our base-case estimate over the broadest range that seemed plausible. The probabilities used in baseline analyses and the ranges evaluated in sensitivity analyses are listed in Table 1.

Results

Impact of CPM on LE

The predicted remaining LEs for women undergoing CPM and no CPM are presented according to age, stage, and ER status at primary breast cancer diagnosis (Table 2). LE gain from CPM ranged from 0.13 to 0.59 years for women with stage I breast cancer and 0.08 to 0.29 years for those with stage II breast cancer. CPM was more beneficial among younger women and those with stage I and ER-negative breast cancer. Forty-year-old women with stage I ER-negative breast cancer will live on average 36.44 years with no CBC and 0.32 years with CBC (lifetime risk of CBC is 1.8%) if they choose CPM; if they did not choose CPM, they would live 33.20 years with no CBC and 2.97 years with CBC (lifetime risk of CBC is 16.4%). Thus, although women will live on average 0.59 years longer with CPM than without, much of that time is spent without CBC and with only the negative impact of CPM. The potential benefit of CPM was consistently lower for patients with stage II breast cancer because of the worse prognosis associated with the primary breast cancer. Similarly, the potential benefits of CPM are more modest for older women because they have relatively fewer years of remaining LE. Sixty-year-old women will gain less than 2 months in LE from CPM, whereas 40-year-old women will gain as much as 7 months. CPM for ER-negative breast cancer patients is more beneficial because the probability of developing a CBC is higher among these women compared with ER-positive breast cancer patients.

Impact of CPM on Survival

The predicted absolute 10- and 20-year overall and disease-free survival differences projected for CPM vs no CPM are shown in Table 2. Twenty-year survival differences ranged from 0.56% to 0.94% for women with stage I breast cancer and 0.36% to 0.61% for women with stage II breast cancer, depending on age and ER

Table 1. Base-case probabilities and ranges evaluated in sensitivity analysis

Variable	% (range)	Source
Primary breast cancer		
10-year disease specific mortality		(21,22)
Stage I	1.8	
Stage II	23.1	
Stage III	59.2	
Stage IV	91.1	
Contralateral breast cancer		
Yearly incidence		(23–26)
Hormone receptor positive	0.4 (0.2–0.6)	
Hormone receptor negative	0.5 (0.3–0.7)	
Disease stage at diagnosis		(13,22,27)
Stage I	67 (47–67)	
Stage II	24 (24–41)	
Stage III	5 (5–7)	
Stage IV	4 (4–5)	
Contralateral prophylactic mastectomy		(10–14)
Breast cancer risk reduction	90 (80–100)	

Table 2. Predicted life expectancy gains, absolute overall survival difference, and absolute disease-free survival difference from contralateral prophylactic mastectomy*

Cohort (age, y; ER status; stage)	Life expectancy, y			20-y (10-y) survival, %	
	CPM	No CPM	LE gain	Absolute overall difference	Absolute disease-free difference
40, ER+, stage I	36.77	36.30	0.47	0.76 (0.25)	5.81 (3.39)
40, ER–, stage I	36.76	36.17	0.59	0.94 (0.31)	7.20 (4.22)
40, ER+, stage 2	24.16	23.92	0.24	0.49 (0.20)	3.73 (2.66)
40, ER–, stage 2	24.15	23.86	0.29	0.61 (0.25)	4.62 (3.30)
50, ER+, stage 1	29.72	29.45	0.27	0.70 (0.25)	5.33 (3.31)
50, ER–, stage 1	29.71	29.38	0.33	0.87 (0.31)	6.60 (4.12)
50, ER+, stage 2	20.89	20.74	0.15	0.45 (0.19)	3.43 (2.60)
50, ER–, stage 2	20.88	20.70	0.18	0.56 (0.24)	4.24 (3.22)
60, ER+, stage 1	22.54	22.41	0.13	0.56 (0.23)	4.25 (3.11)
60, ER–, stage 1	22.53	22.37	0.16	0.69 (0.29)	5.26 (3.87)
60, ER+, stage 2	16.98	16.90	0.08	0.36 (0.18)	2.73 (2.44)
60, ER–, stage 2	16.98	16.88	0.10	0.44 (0.23)	3.38 (3.03)

* CPM = contralateral prophylactic mastectomy; ER = estrogen receptor; LE = life expectancy.

status. No cohort of women had a greater than 1% absolute survival difference at 20 years.

Twenty-year disease-free survival differences ranged from 4.25% to 7.20% for women with stage I breast cancer and 2.73% to 4.62% for women with stage II breast cancer, depending on age and ER status. The overall survival and disease-free survival curves for 40-year-old women with stage I breast cancer are shown in Figure 2, A–D.

Sensitivity Analyses

CPM and CBC. The predicted absolute 20-year survival differences for 40-year-old women with stage I breast cancer with varying probabilities of CBC (annual risk of 0.2% to 0.7%) and CPM effectiveness (80% to 100%) are shown in Figure 3. Greater survival benefits were seen with greater CPM effectiveness and with a higher annual probability of developing CBC. The largest absolute survival difference was 1.45% when the CPM effectiveness was 100% and the annual probability of developing CBC was 0.7% per year.

Similar findings were observed when varying age and stage. The survival benefit ranged from 0.22% to 0.93% for 40-year-old

women with stage II breast cancer; 0.31% to 1.3% and 0.20% to 0.86% for 50-year-old women with stage I or II breast cancer, respectively; and 0.25% to 1.06% and 0.16% to 0.68% for 60-year-old women with stage I and II breast cancer, respectively.

Projected survival benefit from CPM was more sensitive to variations in the risk of CBC than variations in the effectiveness of CPM. For example, for 40-year-old women with stage I breast cancer, the survival difference ranged from 0.81% to 1.03% when varying the risk of CBC at constant CPM effectiveness, whereas varying CPM effectiveness at constant annual probability of developing CBC resulted in survival differences ranging from 0.09% to 0.3%.

Stage of CBC. We varied the probability of developing CBC stage I from 67% to 47%, stage II from 24% to 41%, stage III from 5% to 7%, and stage IV from 4% to 5%. Using these parameters, the predicted 20-year absolute survival difference for 40-year-old women with stage I ER-negative breast cancer changed from 0.94% (base-case) to 1.30%; ER-positive breast cancer changed from 0.76% to 1.04%. Similar 20-year survival changes were observed

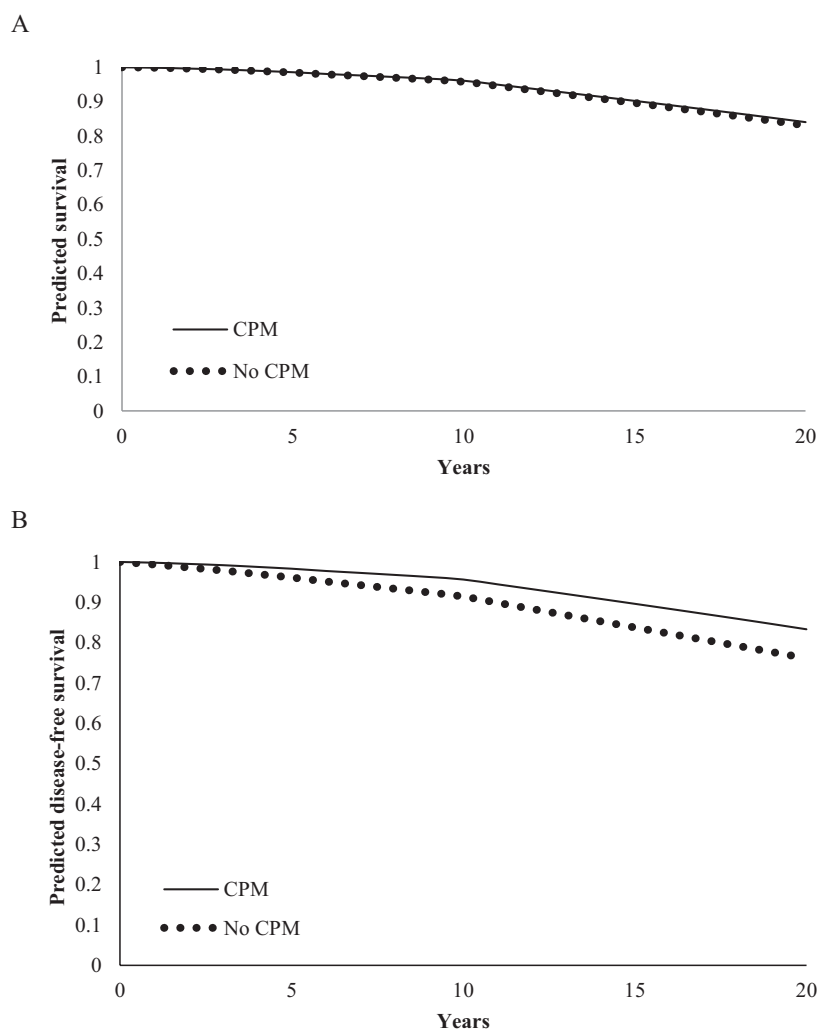


Figure 2. Twenty-year predicted overall survival and disease-free survival in 40-year-old women with stage I breast cancer. **A)** Overall survival in estrogen receptor-negative stage I breast cancer. **B)** Disease-free survival in estrogen receptor-negative stage I breast cancer. **C)** Overall survival in estrogen receptor-positive stage I breast cancer. **D)** Disease-free survival in estrogen receptor-positive stage I breast cancer. CPM = contralateral prophylactic mastectomy.

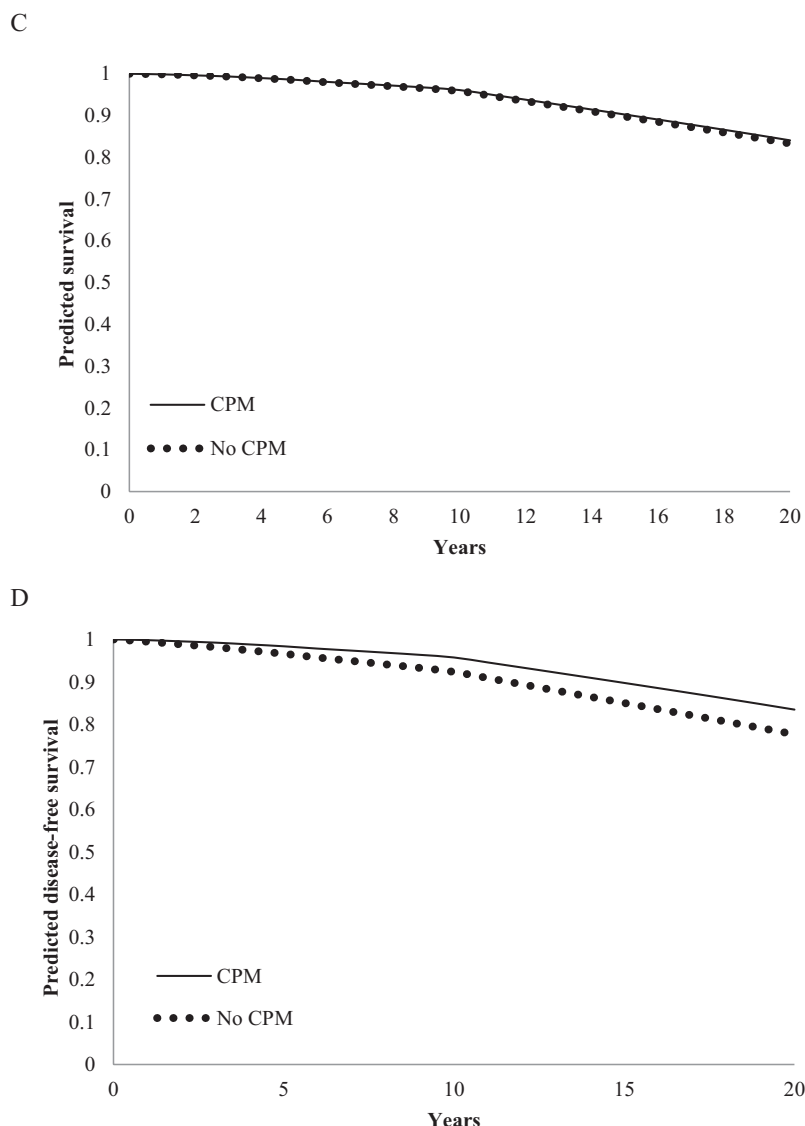


Figure 2. Continued

when varying age, stage, and ER status, although these differences were modest compared with 40-year-old women with stage I breast cancer.

Discussion

In this analysis, we assumed that the only plausible way that CPM improves breast cancer survival is by preventing a potentially fatal CBC. In 2011, the EBCTCG (26) reported that the annual rate of invasive CBC was approximately 0.4% for patients with ER-positive breast cancer treated with tamoxifen and 0.5% for patients with ER-negative breast cancer. All age, tumor, and treatment subgroups had annual rates less than 0.7%. Thus, the 10-year cumulative risk of CBC is approximately 4% to 5%.

The risk of CBC may be even lower for patients diagnosed today. Nichols et al. (31) reported that the rates of metachronous CBC have substantially decreased since 1985 largely because of adjuvant systemic therapies. The risk of CBC for postmenopausal women with ER-positive breast cancer may be lower yet because of the

increased use of aromatase inhibitors. In the Arimidex, Tamoxifen, Alone or in Combination trial, the 10-year cumulative incidence of CBC for women treated with anastrozole was only 3.2% (25).

In addition to the risk of CBC, the potential survival benefit of CPM also depends upon the mortality of the index cancer. In our analysis, we found that the LE gain after CPM was lower for patients with higher-stage tumors. Although we did not model comorbidities, the potential survival benefit of CPM would be less for patients with other competing mortality factors. Also, the stage and mortality of the CBC impacts the potential survival benefit of CPM. The stage of metachronous CBC is usually lower than that of the index cancer. Using a state cancer registry, Quan et al. (27) reported that more than 90% of metachronous cancers were either stage I or II.

Several studies have demonstrated that CPM reduces the risk of CBC by approximately 90% (10–14), but the potential survival benefit is unclear. A recently published Cochrane analysis concluded that “there is insufficient evidence that CPM improves survival” (17). Yet, several retrospective studies have reported a survival benefit after CPM for selected patients. Using the SEER database, Bedrosian

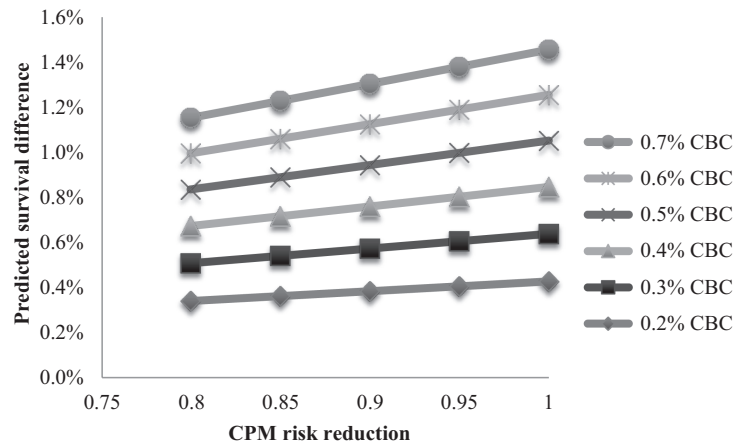


Figure 3. Sensitivity analysis on predicted 20-year absolute survival difference in 40-year old women with stage I breast cancer with varying annual probabilities of developing contralateral breast cancer (CBC) and effectiveness of contralateral prophylactic mastectomy (CPM).

et al. (15) reported that CPM was associated with a 4.8% absolute improvement in 5-year breast cancer-specific survival in young women with early-stage ER-negative breast cancer. In a retrospective single-center study, Boughey et al. (16) reported that CPM was associated with a 9% absolute improvement in 10-year overall survival. In another retrospective single-center study, Peralta et al. (13) reported a 15% absolute improvement in 15-year overall survival. The absolute improvement in overall survival associated with CPM in these studies paradoxically exceeds the expected cumulative incidence of CBC.

The survival benefit reported in our decision analysis was considerably lower than the results of retrospective single-center and cancer database studies. We could identify no cohort in which CPM was associated with a 1% absolute improvement in 20-year survival. The performance of sensitivity analyses varying the rates of CBC, stage of CBC, and CPM effectiveness yielded a maximum survival benefit of only 1.45% at 20 years. We found that the maximum 5- and 10-year absolute survival benefits from CPM were 0.09% and 0.31%, respectively. In contrast, the EBCTCG (32) reported the 5- and 10-year absolute survival benefit from adjuvant chemotherapy in estrogen-poor breast cancer to be 5% and 8%, respectively.

Selection bias markedly limits the ability to compare survival rates between CPM and no CPM patients in retrospective and cancer registry studies. Patient, tumor, and treatment characteristics differ markedly between those who undergo CPM and those who do not. Patients undergoing CPM are generally younger, more likely to be white, have higher education level, have private insurance, and have a family history of breast cancer (1,4,5,33). Tumor characteristics such as infiltrating lobular histology, multicentric disease, and lower breast cancer stage are also associated with higher CPM rates (4,5,34,35). Finally, patients undergoing CPM are more likely to receive breast magnetic resonance imaging, to undergo genetic testing, to receive breast reconstruction, and to be treated at a comprehensive cancer program or teaching institution (1,5,33,35). Similarly, patients who undergo more aggressive surgery are probably healthier and more likely to receive adjuvant therapy. These differences likely explain the paradox of the CPM survival advantage exceeding the cumulative risk of CBC in retrospective studies.

Our analysis has several limitations. These results do not apply to BRCA gene mutation carriers with unilateral breast cancer who

have a cumulative 10-year risk of CBC of approximately 30% to 40% (36). The outcomes of this analysis were limited to overall and disease-specific survival; we did not evaluate other important outcomes such as surgical complications and quality of life. Also, we assumed the mortality of CBC was the same as the mortality of the index cancer reported by SEER; we added these mortalities into our model once a woman developed CBC. SEER mortality rates include mortality from CBC, and, therefore, we may overestimate the mortality rates in our model. Nevertheless, when comparing survival curves, they are very similar to SEER and likely have little impact on the survival estimates that we found. Another limitation is potential variation in the sources used for our model input. However, the EBCTCG studies and the SEER database use large populations, which likely limits the extent of variation.

Survival is only one potential benefit of a cancer risk-reduction strategy; effects on cancer-related anxiety, cosmesis, and self-image are also important in decision-making processes. For some women, the negative impact of CPM on quality of life may outweigh a potential survival benefit. For others who are very anxious about CBC, CPM may result in a psychological benefit even if survival benefits are minimal. Other investigators have reported quality-of-life utilities (numbers that represent the strength of an individual's preference) for breast-conserving surgery, double mastectomy, and CBC (37,38). Because of the relatively long time spent without CBC with CPM, the difference between the utilities for CPM and no CPM have a large effect on quality-adjusted life years for the two strategies. Decision-making parameters that would increase the likelihood of choosing CPM would be a lower utility for CBC and no CPM and a higher utility for CPM. If a woman places approximately a 3% decrease in the utility for CPM vs no CPM, the quality-adjusted life years would favor no CPM (data not shown). Because our decision model is intended to facilitate decision-making by individuals, we have not adjusted for quality of life because utility values are highly variable between women. We present our results in terms of LE and survival differences to help individual women incorporate these effects and make personal assessments of how these interventions would affect their lives.

One prospective survey study reported that women with newly diagnosed breast cancer substantially overestimated their risk of

developing CBC (9). Another survey study suggested that breast cancer patients have unrealistic expectations of the benefits of CPM (39). Perhaps, these perceptions partially explain the dramatic increase in CPM rates observed in the United States. Survival estimates derived from our model may be useful for physicians and breast cancer patients to arrive at evidence-based informed decisions regarding CPM. Moreover, the use of accurate and easily understood decision aids may reverse some of the mastectomy trends recently observed in the United States.

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Notes

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