Survival Outcomes after Contralateral Prophylactic Mastectomy: A Decision Analysis

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Pamela R. Portschy, M.D.

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Todd M. Tuttle, M.D., M.S., Advisor

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Dedication

This thesis is dedicated to all my academic and clinical mentors who have given their time and effort to help me succeed.

Abstract

Background: Contralateral prophylactic mastectomy (CPM) rates have significantly 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%.

Conclusion: 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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INTRODUCTION

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 about 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. 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; appendix). The model simulates the long-term prognosis of hypothetical cohorts of women with newly diagnosed unilateral breast cancer under two scenarios: (1) CPM (i.e., double mastectomy) and (2) no CPM (assuming that women undergo either lumpectomy with radiation therapy 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 following 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 (i.e., 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 life expectancy (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 SEER. [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 (i.e., 1- 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. 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 about 0.4% for patients with ER-positive breast cancer treated with tamoxifen and about 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.

Contralateral Breast Cancer Stage. Using the Oregon State Cancer Registry database, Quan et al. [27] reported that over 90% of CBC's were either ductal carcinoma in situ (DCIS) 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 DCIS. We estimated that the probability of developing stage I CBC was 67%, stage II was 24%, stage III was 5%, and stage IV 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 the

survival benefit of bilateral mastectomies (i.e., 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 (e.g., stage of CBC), we varied our base-case estimate over the broadest range that seemed plausible.

RESULTS

Impact of CPM on LE

The predicted remaining LE's 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, while 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 as the probability of developing a CBC is higher amongst these women compared to ER-positive breast cancer patients.

Impact of CPM on survival

The predicted absolute 10 and 20-year 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 status. No cohort of women had a greater than 1% absolute survival difference at 20 years.

The predicted absolute 10 and 20-year disease-free survival differences are shown in Table 2. 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.

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 when varying age, stage, and ER status; although these differences were modest compared to 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 about 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 about 4-5%.

The risk of CBC may be even lower for patients diagnosed today. Nichols et al. [31] reported that the rates of metachronous CBC have significantly 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 (ATAC) 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 didn't model co-morbidities, 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 about 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 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 benefit from CPM was 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 was 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 significantly 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 a breast MRI, 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 about 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 (QALY's) 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 about a 3% decrease in the utility for CPM vs. no CPM the QALY's 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, as 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.

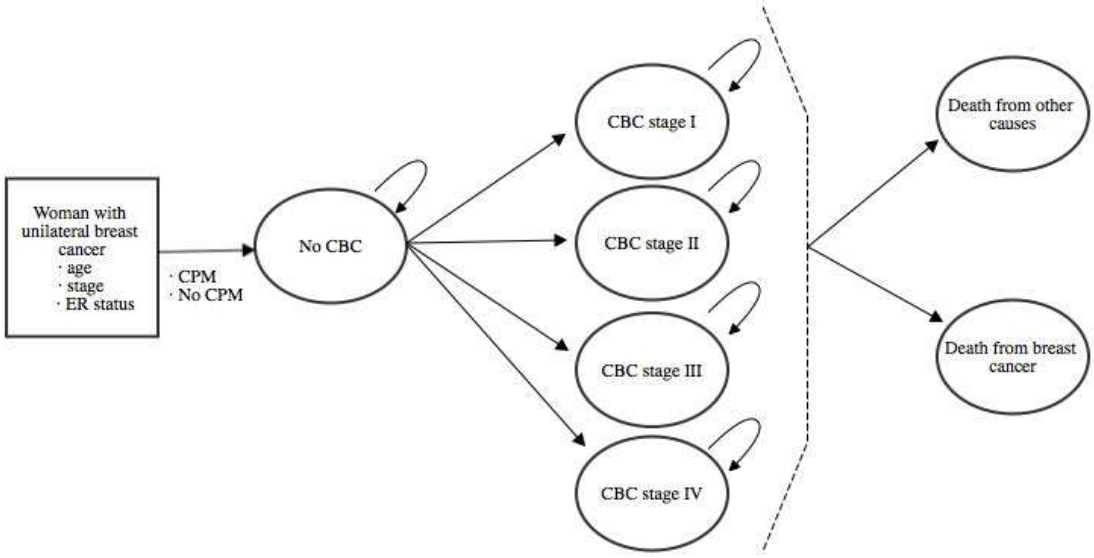


Figure 1: Markov Model. Abbreviations: ER, estrogen receptor; CPM, contralateral prophylactic mastectomy; CBC, contralateral breast cancer. Women in each Markov state (no CBC, CBC stage I, CBC stage II, CBC stage III, CBC stage IV) can die from other causes or die from breast cancer. Each cycle of the Markov model is one year. The model ran the lifetime of the cohort. For example, the model predicting life expectancy in the 40 year-old 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.

Table 1. Base-Case Probabilities and Ranges Evaluated in Sensitivity Analysis

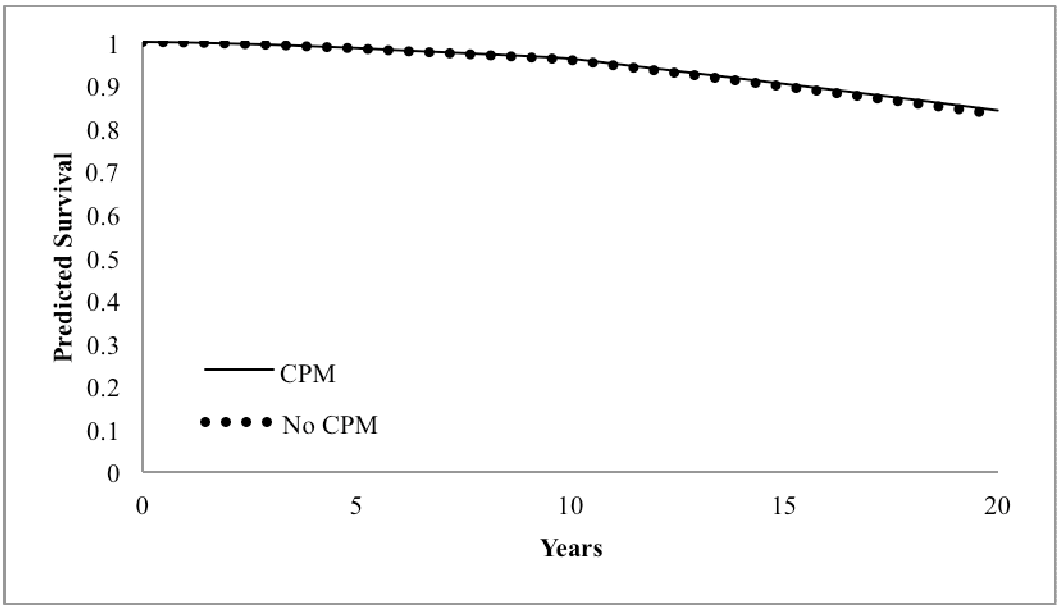
Variable	% (Range)	Source
Primary breast cancer		
10-year disease specific mortality		[21, 22]
Stage I	1.8	
Stage II	23.1	
Stage III	59.2	
Stage IV	91.1	
Contralateral breast cancer		
Yearly incidence		[23-26]
Hormone receptor positive	0.4 (0.2-0.6)	
Hormone receptor negative	0.5 (0.3-0.7)	
Disease stage at diagnosis		[13, 22,
Stage I	67 (47-67)	27]
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 Survival Difference, and Absolute Disease- Free Survival Difference from Contralateral Prophylactic Mastectomy

	Life Expectancy (yrs)			20 year (10 year) Survival (%)	
Cohorts	**CPM**	**No CPM**	**LE Gain**	**Absolute Overall Difference**	**Absolute Disease-Free Difference**
40 yo, ER+, Stage I	36.77	36.30	0.47	0.76 (0.25)	5.81 (3.39)
40 yo, ER-, Stage I	36.76	36.17	0.59	0.94 (0.31)	7.20 (4.22)
40 yo, ER+, Stage 2	24.16	23.92	0.24	0.49 (0.20)	3.73 (2.66)
40 yo, ER-, Stage 2	24.15	23.86	0.29	0.61 (0.25)	4.62 (3.30)
50 yo, ER+, Stage 1	29.72	29.45	0.27	0.70 (0.25)	5.33 (3.31)
50 yo, ER-, Stage 1	29.71	29.38	0.33	0.87 (0.31)	6.60 (4.12)
50 yo, ER+, Stage 2	20.89	20.74	0.15	0.45 (0.19)	3.43 (2.60)
50 yo, ER-, Stage 2	20.88	20.70	0.18	0.56 (0.24)	4.24 (3.22)
60 yo, ER+, Stage 1	22.54	22.41	0.13	0.56 (0.23)	4.25 (3.11)
60 yo, ER-, Stage 1	22.53	22.37	0.16	0.69 (0.29)	5.26 (3.87)
60 yo, ER+, Stage 2	16.98	16.90	0.08	0.36 (0.18)	2.73 (2.44)
60 yo, ER-, Stage 2	16.98	16.88	0.10	0.44 (0.23)	3.38 (3.03)

Abbreviations: CPM, contralateral prophylactic mastectomy; LE, life expectancy; ER+, estrogen receptor positive; ER -, estrogen receptor negative; yo, year old; yrs, year

A.


Predicted Survival
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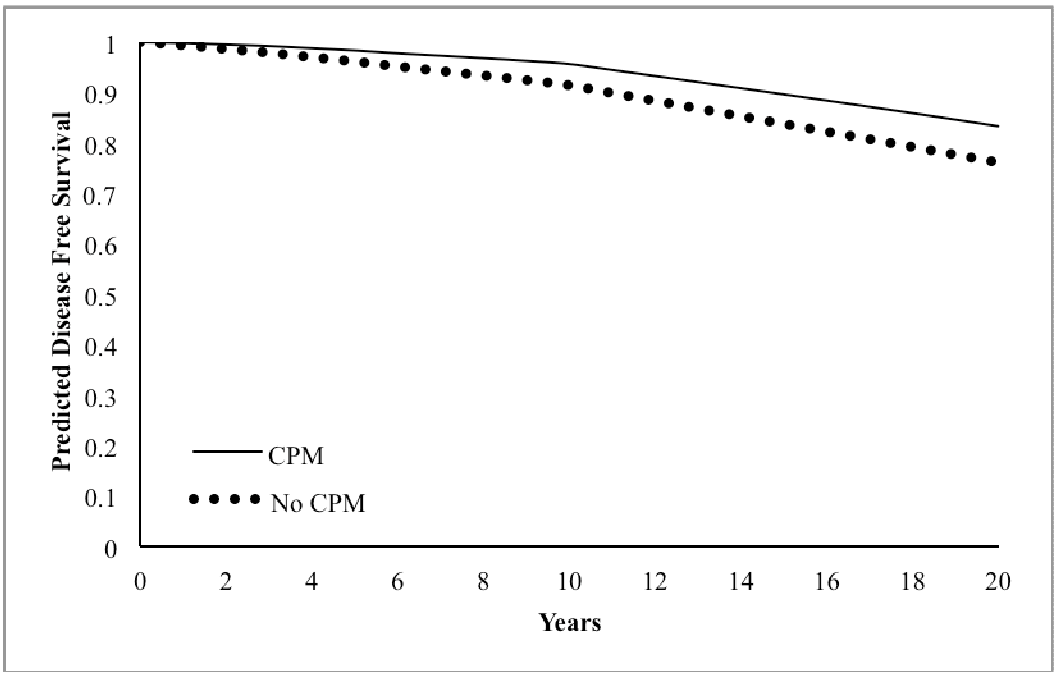
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
CPM
No CPM
0
5
10
15
20
Years

B.


Predicted Disease Free Survival
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0.8
0.7
0.6
0.5
0.4
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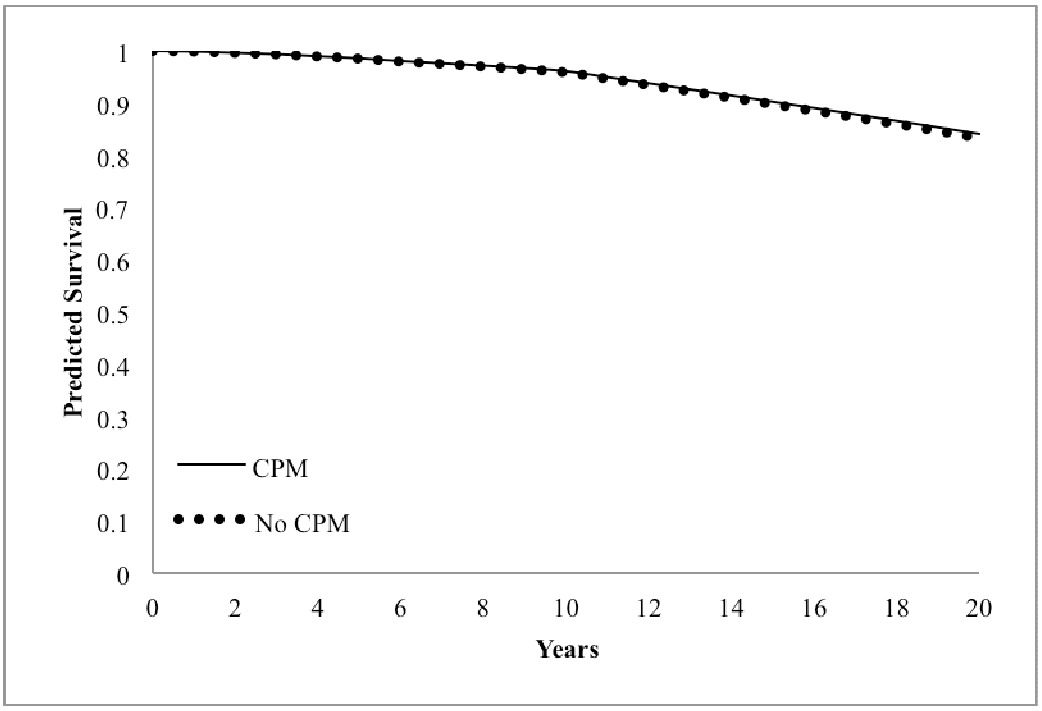
C.



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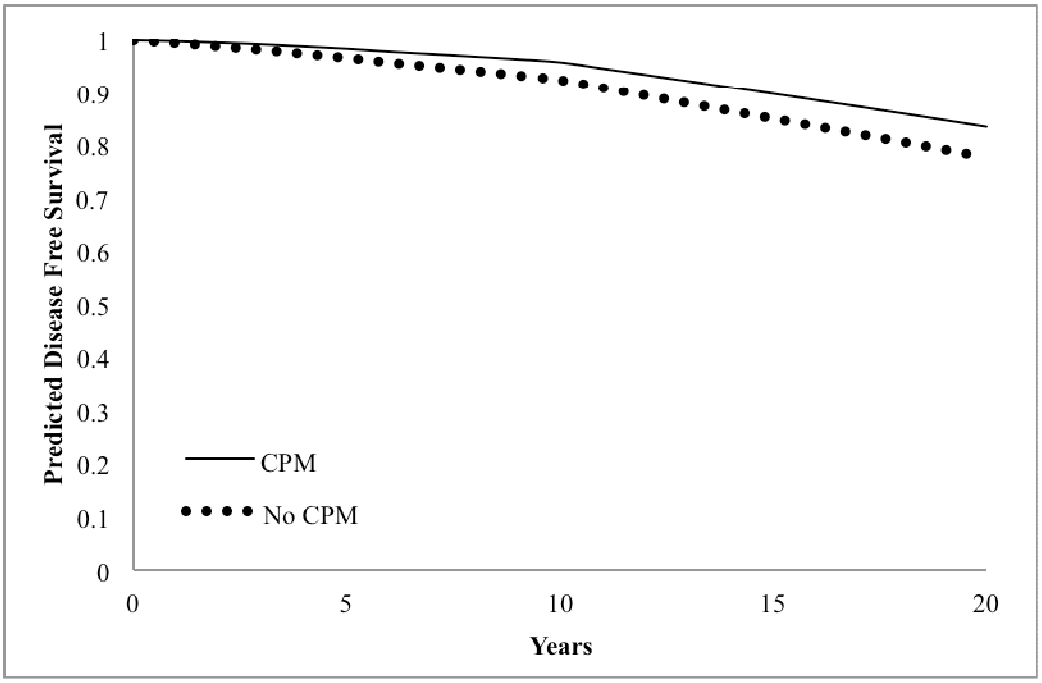

Figure 2: Twenty-year predicted overall survival and disease-free survival in 40 year-old women with stage I breast cancer. A, Overall survival in estrogen receptor negative stage I breast cancer. B, Disease-free survival in estrogen receptor negative stage I breast cancer. C, Overall survival in estrogen receptor positive stage I breast cancer. D, Disease-free survival in estrogen receptor positive stage I breast cancer.

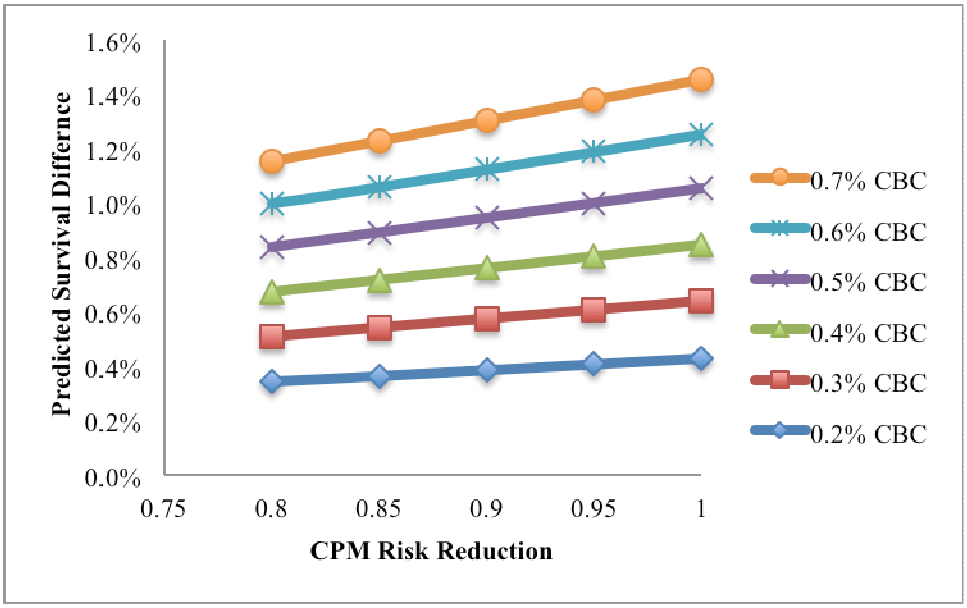

Figure 3. Sensitivity analysis on predicted twenty-year absolute survival difference in 40-year old women with stage I breast cancer with varying annual probabilities of developing contralateral breast cancer (CBC) and effectiveness of contralateral prophylactic mastectomy (CPM).

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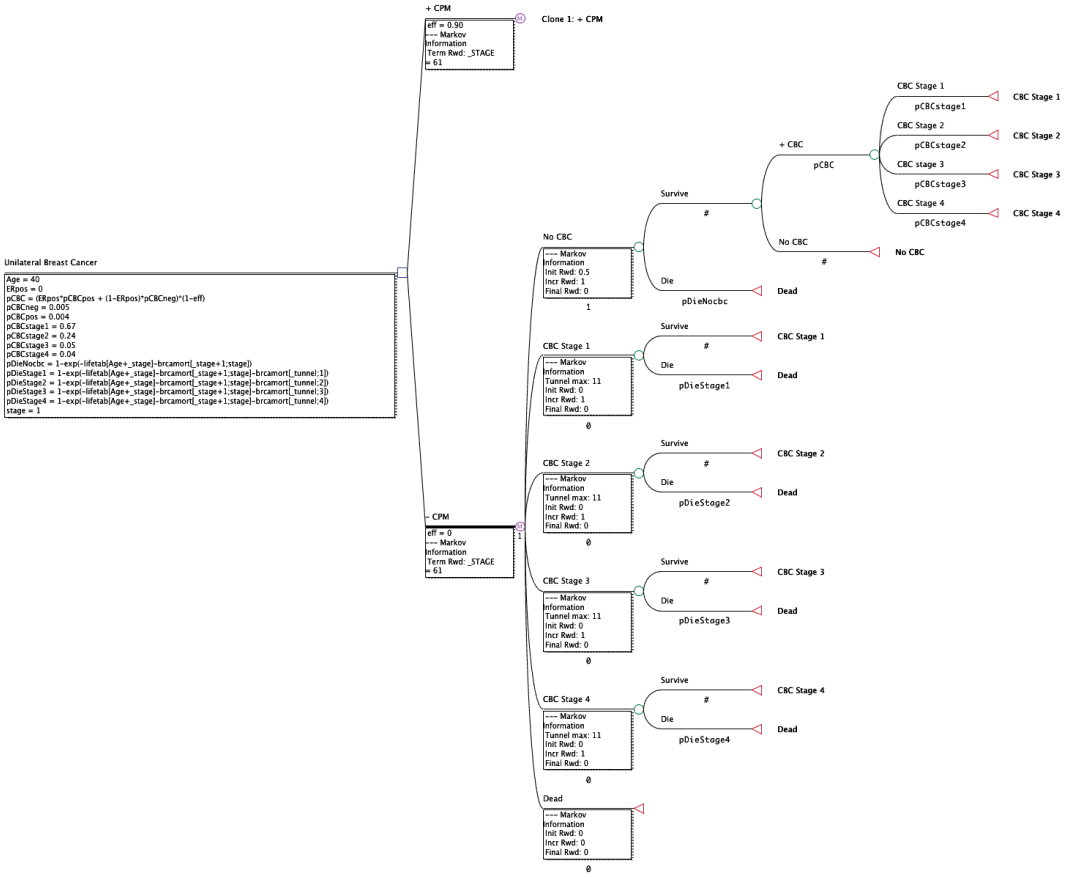
Appendix

Markov Model:



Abbreviations: stage, variable used for stage of breast cancer; _STAGE, model counter, each cycle is one year, for example first cycle time = 0, second cycle time = 1.
ER, estrogen receptor; CPM, contralateral prophylactic mastectomy;
CBC, contralateral breast cancer; eff, effective of contralateral prophylactic mastectomy

brcamort, Breast Cancer Mortality Table:

Time (years)	Stage 1	Stage 2	Stage 3	Stage 4
1	0	0.007024615	0.087738914	0.515838166
2	0.0010005	0.029639369	0.14167425	0.328131905
3	0.001001502	0.03375848	0.125834228	0.304883435
4	0.002006019	0.033827557	0.10837663	0.257643563
5	0.002010051	0.032715834	0.09150186	0.233400051
6	0.003022672	0.026730238	0.085428848	0.186453794
7	0.002020203	0.027464413	0.076885143	0.168749479
8	0.002024292	0.024511031	0.056917363	0.150480951
9	0.002028398	0.021317422	0.064972455	0.157003749
10	0.003050333	0.025675351	0.057158414	0.116533816
11+	0.008719655	0.02855171	0.037291251	0.077214113

lifetab, 2008 U.S. Women Life Table:

40	0.001349991
41	0.001485824
42	0.001643086
43	0.001820129
44	0.002008175
45	0.002198728
46	0.002390109
47	0.002587726
48	0.002797324
49	0.003022516
50	0.003269711
51	0.003530327
52	0.003792993
53	0.004052078
54	0.004317881
55	0.004599621
56	0.004922169
57	0.005309455
58	0.005781141
59	0.006331949
60	0.006955423
61	0.007629364
62	0.008340312
63	0.009080023
64	0.009872359
65	0.010786443

66	0.011838922
67	0.012979695
68	0.014178268
69	0.015473447
70	0.016880352
71	0.018547232
72	0.02047223
73	0.022630014
74	0.024950558
75	0.027424561
76	0.030211367
77	0.033370463
78	0.037086502
79	0.041297081
80	0.045886804
81	0.050882598
82	0.056705728
83	0.063777195
84	0.071586555
85	0.080427769
86	0.090940935
87	0.102714297
88	0.115824094
89	0.130373073
90	0.146459453
91	0.164173422
92	0.183592933
93	0.20477919
94	0.227771802
95	0.252584036
96	0.279198097
97	0.307561326
98	0.337583002
99	0.369133107
100	1000