Cost-Effectiveness of Contralateral Prophylactic Mastectomy Versus Routine Surveillance in Patients With Unilateral Breast Cancer

Benjamin Zendejas, James P. Moriarty, Jamie O'Byrne, Amy C. Degnim, David R. Farley, and Judy C. Boughey

From the Mayo Clinic, Rochester, MN.

Submitted March 1, 2011; accepted April 12, 2011; published online ahead of print at www.jco.org on June 20, 2011.

Supported by Grant No. 1 UL1 RR024150 from the National Center for Research Resources, a component of the National Institutes of Health (NIH), and the NIH Roadmap for Medical Research. B.Z. is a recipient of the American Society of Clinical Oncology Foundation Merit Award.

Presented at the American Society of Clinical Oncology Breast Cancer Symposium, October 1-3, 2010, Washington, DC, and at the Society of Surgical Oncology's 64th Annual Cancer Symposium, March 2-5, 2011, San Antonio, TX.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official view of National Center for Research Resource or the National Institutes of Health.

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

Corresponding author: Judy C. Boughey, MD, Department of Surgery, Mayo Clinic, 200 First St SW, Rochester MN, 55905; e-mail: boughey.judy@mayo.edu.

© 2011 by American Society of Clinical Oncology

0732-183X/11/2922-2993/\$20.00

DOI: 10.1200/JCO.2011.35.6956

ABSTRACT

Purpose

Contralateral prophylactic mastectomy (CPM) rates in women with unilateral breast cancer are increasing despite controversy regarding survival advantage. Current scrutiny of the medical costs led us to evaluate the cost-effectiveness of CPM versus routine surveillance as an alternative contralateral breast cancer (CBC) risk management strategy.

Methods

Using a Markov model, we simulated patients with breast cancer from mastectomy to death. Model parameters were gathered from published literature or national databases. Base-case analysis focused on patients with average-risk breast cancer, 45 years of age at treatment. Outcomes were valued in quality-adjusted life-years (QALYs). Patients' age, risk level of breast cancer, and quality of life (QOL) were varied to assess their impact on results.

Results

Mean costs of treatment for women age 45 years are comparable: \$36,594 for the CPM and \$35,182 for surveillance. CPM provides 21.22 mean QALYs compared with 20.93 for surveillance, resulting in an incremental cost-effectiveness ratio (ICER) of \$4,869/QALY gained for CPM. To prevent one CBC, six CPMs would be needed. CPM is no longer cost-effective for patients older than 70 years (ICER \$62,750/QALY). For *BRCA*-positive patients, CPM is clearly cost-effective, providing more QALYs while being less costly. In non-*BRCA* patients, cost-effectiveness of CPM is highly dependent on assumptions regarding QOL for CPM versus surveillance strategy.

Conclusion

CPM is cost-effective compared with surveillance for patients with breast cancer who are younger than 70 years. Results are sensitive to *BRCA*-positive status and assumptions of QOL differences between CPM and surveillance patients. This highlights the importance of tailoring treatment for individual patients.

J Clin Oncol 29:2993-3000. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Breast cancer is the most common malignancy in women, with 192,000 estimated new cases occurring annually in the United States.¹ In recent years, breast-conserving therapy (BCT) has become the treatment of choice, resulting in fewer women undergoing unilateral mastectomy. Within this context, however, a recent increased trend in the use of contralateral prophylactic mastectomy (CPM) as a risk reduction strategy for contralateral breast cancer (CBC) has been observed nationally.²⁻⁵

Women treated for unilateral breast cancer carry an estimated annual risk of 0.5% to 1.0% of developing a CBC.⁶ Women often perceive that their risk of CBC is greater than this and struggle with the decision of how to manage their contralat-

eral breast. They can either choose to undergo routine surveillance of their contralateral breast or undergo CPM. Although CPM has been shown to decrease the risk of CBC by 90% to 95%,⁷⁻⁹ the ability of CPM to prolong survival is controversial; indeed most data show no overall survival benefit for the majority of women.¹⁰

Substantial long-term costs are incurred with routine surveillance of the contralateral breast. These costs include but are not limited to regular physician visits, imaging studies (mammography, and where indicated, ultrasonography and magnetic resonance imaging [MRI]), possible diagnostic biopsies, and eventually the inherent possibility of developing and having to treat a CBC, which introduces more associated costs (surgery, radiation, chemotherapy, and so on) and its psychological burden. Conversely, the

Fig 1. Markov model. Patients could transition into death from other causes from any of the four living states (disease-free, contralateral breast cancer [CBC], recurrent cancer, metastatic cancer). Once a patient is in the metastatic state, that patient could not transition to any other living health state. Only patients in the metastatic state could transition to death from disease. All patients were assumed to start the model in the disease-free health state after the index breast cancer treatment. CPM, contralateral prophylactic mastectomy.

costs involved with CPM are related to the procedure itself and its associated short- and long-term morbidity, along with follow-up physician visits; however, no long-term imaging surveillance is required and the risk of developing a CBC is substantially decreased. We sought to determine whether CPM is a cost-effective alternative to routine surveillance as a risk-management strategy for CBC. We hypothesized that CPM would be a cost-effective alternative for younger patients, but not for all patients with breast cancer.

METHODS

Using decision analytic software (TreeAge Pro 2009; TreeAge Software, Williamstown, MA), we constructed a Markov model (Fig 1) to estimate and compare the direct medical costs and health outcomes associated with two CBC risk management strategies for patients with early-stage, node-negative, unilateral breast cancer: unilateral mastectomy followed by either surveillance (standard of care) or CPM. Six distinct and mutually exclusive health states were considered: disease-free, locally recurrent breast cancer, CBC, metastatic breast cancer, death as a result of disease, death as a result of other causes. The study was considered exempt by the Mayo Clinic institutional review board.

Main model assumptions are illustrated in Figure 2. We assumed that women who underwent CPM had a mastectomy, as opposed to BCT, as

treatment of their index breast cancer because it is unusual for women to consider CPM if they opt for BCT. After breast cancer treatment, all patients would be considered disease-free and be seen by a physician every 6 months during the first 5 years and yearly thereafter, unless they developed a new episode of breast cancer, at which point they would return to the same initial post-breast cancer treatment follow-up pattern.¹¹ In addition to physician visits, patients in the surveillance group would also undergo annual mammography with computer-aided detection. Surveillance patients developing a CBC were assumed to undergo a unilateral mastectomy for treatment of the new contralateral cancer. Diagnostic tests that identified and confirmed the new CBC were assumed to be mammography with computer-aided detection, ultrasonographic-guided biopsy with associated pathology, and breast MRI. CPM patients developing a CBC (occurrence of breast cancer at the CPM site) would undergo wide local excision of the chest wall mass and would undergo similar diagnostic and confirmatory testing similar to that of those patients in the routine surveillance strategy, with the exception of mammographic imaging.

In either strategy, patients who developed a local recurrence on the side of their index breast cancer were assumed to undergo wide local

Table 1. Estimates Used in the Markov Model

Variable	Base-Case Estimate	Reference
Annual transition probabilities, %		
CBC (CPM)	0.03	7-9,12
CBC (surveillance)	0.6	6,7,13,14
CBC (BRCA positive, CPM)	0.4	9,15,16
CBC (BRCA positive, surveillance)	4	17,18
Local recurrence	0.63	SEER ¹⁹
Metastatic cancer	1.25	SEER ¹⁹
Death from metastatic disease	25.21	SEER ¹⁹
Death from other causes	Age-specific	National Vital Statistics ²⁰
Costs,* US\$		
Physician office visit (99214)	97.78	www.cms.hhs.gov ²¹
Breast biopsy (19102)	203.13	www.cms.hhs.gov ²¹
Breast ultrasound (76645)	98.16	www.cms.hhs.gov ²¹
Breast MRI (77059)	888.70	www.cms.hhs.gov ²¹
PET (78813)	101.94	www.cms.hhs.gov ²¹
CT chest (74150)	274.38	www.cms.hhs.gov ²¹
CT abdomen (71250)	288.02	www.cms.hhs.gov ²¹
Bone scan (78306)	257.70	www.cms.hhs.gov ²¹
Unilateral mammogram (77055)	87.16	www.cms.hhs.gov ²¹
Computer-aided detection (77051)	10.23	www.cms.hhs.gov ²¹
Chemotherapy†	10,963.77	www.cms.hhs.gov ²¹
Radiation therapy‡	14,071.18	www.cms.hhs.gov ²¹
Bilateral simple mastectomy (85.42)	12,668	2007 NIS database ²²
Unilateral simple mastectomy (85.41)	8502	2007 NIS database ²²
Wide local excision (85.21)	8446	2007 NIS database ²²
Death from disease	46,329	10,23-27
Death from other causes	34,257	27

Abbreviations: CBC, contralateral breast cancer; CPM, contralateral prophylactic mastectomy; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging; NIS, Nationwide Inpatient Sample; SEER, Surveillance, Epidemiology, and End Results.

*Numbers in parentheses are Current Procedural Terminology, 4th edition (CPT4)/International Classification of Diseases, 9th revision codes.

†Four cycles of doxorubicin, cyclophosphamide, and pegfilgrastim followed by four cycles of paclitaxel and pegfilgrastim (CPT4 codes: J9000, J9070, J2505, 96413, 96372, 96415, 96411, J8499, J1626, J9265, J1100, J3490, J1200, 96367, 96375).

‡Thirty-day treatment regimen (CPT4 codes: 77263, 77336, 77014, 77290, 77334, 77315, 77300, 77427, 77413, 77321).

Fig 2. Flow diagram of model assumptions and transitions. (*) Every 6 months for the first 5 years after treatment and yearly thereafter $\pm$ every 6 months until death. C, contralateral prophylactic mastectomy strategy only; CAD, computer-aided detection; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; S, surveillance strategy only; US, ultrasound.

excision of the chest wall mass. Diagnostic testing for a recurrence would include ultrasonographic-guided biopsy with associated pathology, chest MRI, and positron emission tomography imaging. After operative treatment, patients with a local recurrence were assumed to undergo chemotherapy and radiation therapy. Patients who developed metastatic cancer were assumed to undergo similar diagnostic work-up as prompted by a recurrence, with the addition of thoracoabdominal computed tomography imaging and bone scans. The diagnostic and therapeutic costs of each health state were assumed to only occur at the transition point and not in subsequent years in the health state. No treatment differences were assumed between the CPM or surveillance strategy in the locally recurrent or metastatic cancer state.

The development of CBC or a local recurrence was based on yearly rates of developing either a new CBC or an ipsilateral breast cancer recurrence (Table 1). Both events, locally recurrent cancer and CBC, would get treated the same year of diagnosis. Patients developing metastatic disease would not transition back to disease-free status and would remain in the metastatic disease state until death, incurring both palliative therapy costs and end-of-life care expenses (ie, inpatient, outpatient, nursing facility, supportive medications, and hormone, chemo, and/or radiation therapy).²³⁻²⁶

We assumed that although a new CBC would be diagnosed as an early-stage breast cancer, the yearly probability of metastatic disease would become cumulative as two low-stage breast cancers are thought to have additive detrimental effects on survival.^{29,30} Similarly, patients who develop a local recurrence would subsequently have a cumulative probability of metastatic disease. In other words, a woman who has had two breast cancers (either an index breast cancer and a CBC or an index breast cancer and a local recurrence) would have a higher probability of developing metastatic disease than women who have had only one breast cancer episode.

Each Markov cycle in the simulation was assumed to last 1 year. Simulations consisted of 10,000 individual patients starting from the index breast cancer and moved through the model until death. Half-cycle corrections were accounted for in the model.³¹ Costs were discounted using a 3% annual discount rate.³²

Transition Parameters

Transition parameters were gathered from published literature or publicly available national databases (Table 1). The transition rate into death from other causes was based on 2004, age-adjusted female mortality rates from the National Vital Statistics database.²⁰

Cost Parameters

Costs were based on the perspective of the health care provider, which included direct costs of medical care related to breast cancer treatment. Costs were categorized by those that occurred in an inpatient or outpatient setting. Inpatient and outpatient costs were obtained from the Nationwide Inpatient Sample database²² and from 2007 rates for Medicare reimbursement,²¹ respectively (Table 1). All costs are presented in 2007 US dollars.

Quality-of-Life Parameters

Quality-of-life adjustment was incorporated into the model on the basis of age-specific health preferences using the concept of utility. Utility theory values quality of life on the basis of individual preferences of various health states.³³ The quality-of-life adjustment is represented in the form of quality-adjusted life-years (QALYs). One QALY would represent 1 year spent in perfect health, whereas a year spent in all other health states would be some fraction of a QALY. Age-specific health preferences (utility weights) for each health state were obtained from published literature (Table 2).^{28,34} Similar to Stout et al,²⁸ we assumed that patients had a utility weight inferior to that of the healthy state for the first 2 years after cancer treatment, after which they would return to having a healthy state utility weight, as long as they did not transition into another health state. New CBCs and recurrent cancers were assumed to have the same utility weights. Patients in the CPM and surveillance groups were assumed to have similar utility weights for each health state.^{35,36}

Base-Case Analysis

Patient simulations were started at age 45 years and increased by 5-year increments until age 75 years. Primary outcomes were the mean cost of lifetime

Table 2. Utility Weights for the Markov Model

Age (years)	Disease Free	Breast Cancer	Local Recurrence	Metastatic Disease	Reference
45-49	0.804	0.724	0.603	0.482	28
50-54	0.780	0.702	0.585	0.468	28
55-59	0.747	0.672	0.560	0.448	28
60-64	0.745	0.670	0.558	0.447	28
65-69	0.734	0.660	0.550	0.440	28
70-75	0.716	0.645	0.537	0.430	28

treatment of breast cancer, mean lifetime QALYs, number of CPMs needed to prevent one CBC, and incremental cost-effectiveness ratios (ICERs) comparing CPM with surveillance. The threshold we used for determining the cost-effectiveness of CPM was \$50,000 per QALY gained; we based this assumption on the report from the Commission on Macroeconomics and Health, which

defines interventions with a cost-effectiveness ratio that is less than the per capita gross domestic product (\$46,381 for the United States in 2009)³⁷ as “very cost-effective.”³⁸ Secondary outcomes were total life-years spent in each health state, number of patients dying as a result of disease, and average life expectancy.

Table 3. Main Results

Age at Treatment (years) and Analysis	CPM		Surveillance		Differences		
	Cost	QALY	Cost	QALY	Cost	QALY	C/E*
Base-case analysis							
45	\$36,594	21.22	\$35,182	20.93	\$1,412	0.29	\$4,869
50	\$37,457	18.72	\$35,871	18.49	\$1,586	0.23	\$6,896
55	\$38,069	16.24	\$36,314	16.05	\$1,755	0.19	\$9,237
60	\$38,860	13.80	\$36,780	13.68	\$2,080	0.12	\$17,333
65	\$39,747	11.47	\$37,490	11.39	\$2,257	0.08	\$28,213
70	\$40,746	9.07	\$38,236	9.03	\$2,510	0.04	\$62,750
75	\$41,843	6.84	\$39,041	6.81	\$2,802	0.03	\$93,400
Sensitivity analyses							
Risk of metastasis not cumulative							
45	\$36,250	21.58	\$34,625	21.52	\$1,625	0.06	\$27,083
50	\$37,175	18.95	\$35,403	18.91	\$1,772	0.04	\$44,300
55	\$37,770	16.41	\$35,878	16.37	\$1,892	0.04	\$47,300
60	\$38,755	13.88	\$36,604	13.84	\$2,151	0.04	\$53,775
65	\$39,618	11.51	\$37,246	11.49	\$2,372	0.02	\$118,600
70	\$40,710	9.11	\$38,132	9.09	\$2,578	0.02	\$128,900
75	\$41,797	6.86	\$38,925	6.84	\$2,872	0.02	\$143,600
No end-of-life care costs							
45	\$18,838	21.22	\$17,152	20.93	\$1,686	0.29	\$5,814
50	\$18,702	18.72	\$16,878	18.49	\$1,824	0.23	\$7,930
55	\$18,184	16.24	\$16,210	16.05	\$1,974	0.19	\$10,389
60	\$17,591	13.80	\$15,365	13.68	\$2,226	0.12	\$18,550
65	\$17,157	11.47	\$14,789	11.39	\$2,368	0.08	\$29,600
70	\$16,478	9.07	\$13,895	9.03	\$2,583	0.04	\$64,575
75	\$15,869	6.84	\$13,008	6.81	\$2,861	0.03	\$95,367
BRCA-positive patients							
45	\$37,459	21.13	\$41,820	19.36	−\$4,361	1.77	−\$2,464†
50	\$38,173	18.59	\$41,822	17.23	−\$3,649	1.36	−\$2,683†
55	\$38,815	16.11	\$41,817	15.14	−\$3,002	0.97	−\$3,095†
60	\$39,370	13.72	\$41,659	13.03	−\$2,289	0.69	−\$3,317†
65	\$40,391	11.40	\$42,187	10.94	−\$1,796	0.46	−\$3,904†
70	\$41,301	9.04	\$42,203	8.75	−\$902	0.29	−\$3,110†
75	\$42,194	6.82	\$42,201	6.63	−\$7	0.19	−\$37†
CPM health preference greater than surveillance							
45	\$36,594	22.74	\$35,182	20.93	\$1,412	1.81	\$780
50	\$37,457	20.09	\$35,871	18.49	\$1,586	1.60	\$991
55	\$38,069	17.45	\$36,314	16.05	\$1,755	1.40	\$1,254
60	\$38,860	14.85	\$36,780	13.68	\$2,080	1.17	\$1,778
65	\$39,747	12.37	\$37,490	11.39	\$2,257	0.98	\$2,303
70	\$40,746	9.81	\$38,236	9.03	\$2,510	0.78	\$3,218
75	\$41,843	7.43	\$39,041	6.81	\$2,802	0.62	\$4,519
CPM health preference less than surveillance							
45	\$36,594	19.70	\$35,182	20.93	\$1,412	−1.23	−\$1,148‡
50	\$37,457	17.35	\$35,871	18.49	\$1,586	−1.14	−\$1,391‡
55	\$38,069	15.03	\$36,314	16.05	\$1,755	−1.02	−\$1,721‡
60	\$38,860	12.75	\$36,780	13.68	\$2,080	−0.93	−\$2,237‡
65	\$39,747	10.57	\$37,490	11.39	\$2,257	−0.82	−\$2,752‡
70	\$40,746	8.33	\$38,236	9.03	\$2,510	−0.70	−\$3,586‡
75	\$41,843	6.25	\$39,041	6.82	\$2,802	−0.56	−\$5,004‡

Abbreviations: C/E, incremental cost-effectiveness ratio; CPM, contralateral prophylactic mastectomy; QALY, quality-adjusted life-years.

*Numbers in bold are below the \$50,000 threshold.

†Denotes CPM being both less costly and more effective (dominant).

‡Denotes CPM being both more costly and less effective (dominated).

Sensitivity Analysis

Base-case analyses were replicated for the following changes in assumptions: risk of metastasis not cumulative because of additional cancers, excluding medical costs associated with death and end-of-life care, increasing the risk of breast cancer of the cohort to that of a patient with a positive deleterious mutation in the *BRCA1* or *BRCA2* gene, and changing the disease-free utility weights for CPM by ± 0.05 .

RESULTS

Base-Case Analysis

Mean cost of lifetime, breast cancer–related treatment until death for women age 45 years were \$36,594 for the CPM strategy and \$35,182 for the surveillance strategy (Table 3). The CPM strategy provided 21.22 mean QALYs as compared with 20.93 for the surveillance strategy. This resulted in an ICER of \$4,869 per QALY gained for CPM when compared with routine surveillance.

As age at treatment increases, CPM becomes less cost-effective. CPM is no longer cost-effective for patients 70 years of age or older (Fig 3). For women 45 years of age, on average, both CPM and surveillance patients lived to age 74 years (Table 4). The rate of CBC in the CPM group was 87 per 10,000, whereas the rate in the surveillance group was 1,705 per 10,000. Results are similar as age increases. Given the rates of CBC observed in each group, six CPMs are needed to prevent one CBC.

Sensitivity Analysis

Removing the assumption of a cumulative risk of metastasis for additional nonmetastatic cancer modifies the results, with CPM no longer cost-effective for patients 55 years of age or older. Excluding the costs of end-of-life care has a large impact on mean costs, decreasing the cost of CPM to \$18,838 and surveillance to \$17,152. However, this adjustment had little overall effect on the ICERs.

For *BRCA*-positive patients, the CPM strategy is a “dominant strategy” in that it is less costly (\$37,459 v \$41,820) and provides more QALYs when compared with surveillance (21.13 v 19.36). This observation is true for all ages. Additionally, the mortality rate is 13% greater for the surveillance group, which resulted in a decrease in the mean

Fig 3. Incremental cost-effectiveness ratio by age for patients with average-risk breast cancer. QALY, quality-adjusted life-year.

survival of patients undergoing routine surveillance by 2 years to age 72 years.

Results vary when modifying disease-free utility weights for the CPM group. Assuming that CPM has a superior utility weight to that of surveillance results in CPM being cost-effective for all age ranges. In contrast, assuming that CPM has an inferior utility weight to that of surveillance results in CPM being dominated by the surveillance strategy, in that surveillance is less costly and produces more QALYs. With the exception of *BRCA*-positive patients, sensitivity analyses had little to no effects on secondary outcomes (Table 4).

DISCUSSION

This study represents the first cost-effectiveness analysis comparing CPM with routine surveillance for patients with unilateral breast cancer. Base-case results show CPM to be cost-effective in the younger age groups. As expected, the rate of new contralateral cancers is much less for the CPM group. For the general population of patients with breast cancer, the assumption that the utility weights for the disease-free state for CPM was equal to or greater than that of surveillance was key to CPM being cost-effective. In fact, primary end points favored surveillance when assuming that the disease-free health state for CPM had lower utility weights than that of surveillance. However, when focusing on patients at high risk for developing breast cancer, CPM was dominant (both less costly and producing more QALYs) at all starting ages of patients.

The results of our model are consistent with those of other modeling and clinical studies that show a lack of survival advantage from CPM for the general population of patients with breast cancer.^{7,10,15,39} Our results also highlight the substantial decrease in the number of CBCs after CPM. One must consider that the beneficial impact of such a decrease in new breast cancers is not solely financial, but also has the potential to greatly decrease patients' burden of suffering as well as demands on health care resources resulting from a diagnosis of a second breast cancer. This decrease of risk of a second breast cancer and avoidance of repeat breast cancer treatment, rather than the controversial survival advantage of CPM, is likely the reason behind recent increasing rates of CPM. Women who have already experienced a breast cancer may view the trade-offs between quantity and quality of life differently than cancer-free women and may have lower thresholds for choosing prophylactic surgery to avoid a second cancer,¹⁵ especially in situations when mastectomy is required for the first cancer.

For patients at high risk (*BRCA* positive) of developing a CBC, our study results are consistent with those from Schrag et al.^{15,40} Using similar decision analysis techniques, they showed an increased life expectancy for women with *BRCA* mutations who undergo prophylactic mastectomy, with and without a previous diagnosis of breast cancer. Our results also show a similar trend with regard to age, with gains in life expectancy declining with age at time of prophylactic surgery. Although we did not account for the degree of penetrance of the *BRCA* mutation and therefore the potential variation in CBC risk, the results observed in our study are consistent with a 2-year increase in life expectancy (on average) for *BRCA*-positive patients with breast cancer who undergo CPM at age 45 years.¹⁵

In theory, some patients who undergo CPM could value the quality of their life to be lower, secondary to self-image distress, than if they had chosen surveillance, whereas others could report higher

Table 4. Secondary Outcomes Per Entire Cohort of 10,000 Simulated Patients

Starting Age (years) Cohort and Analysis	Life Expectancy (years, mean)		No. of Deaths From Disease		No. of Deaths From Other Causes		No. of Years Spent in Disease-Free		No. of Years Spent in New Cancer		No. of Years Spent in Recurrent Cancer		No. of Years Spent in Metastatic Cancer	
	CPM	Sur	CPM	Sur	CPM	Sur	CPM	Sur	CPM	Sur	CPM	Sur	CPM	Sur
Base-case analysis														
45	74.3	74.0	3,565	3,793	6,435	6,207	277,564	271,734	87	1,705	1,802	1,796	14,029	14,852
50	76.4	76.1	3,199	3,379	6,801	6,621	249,332	244,596	73	1,564	1,738	1,730	12,538	13,166
55	78.3	78.1	2,748	2,928	7,252	7,072	219,998	215,879	70	1,420	1,506	1,479	11,099	11,829
60	80.0	79.9	2,353	2,461	7,647	7,539	189,650	186,904	65	1,188	1,263	1,238	9,458	9,912
65	82.0	81.9	1,854	1,934	8,146	8,066	161,276	159,330	58	1,002	1,081	1,086	7,504	7,757
70	83.8	83.8	1,564	1,614	8,436	8,386	131,183	129,769	42	889	863	862	6,014	6,233
75	85.8	85.8	1,144	1,181	8,856	8,819	102,646	101,650	25	673	683	688	4,518	4,647
Sensitivity analyses														
Risk of metastasis not cumulative														
45	74.8	74.8	3,286	3,286	6,714	6,714	283,457	281,809	77	1,725	1,840	1,840	12,951	12,951
50	76.7	76.7	2,971	2,971	7,029	7,029	253,365	251,861	71	1,575	1,759	1,759	11,720	11,720
55	78.5	78.5	2,571	2,571	7,429	7,429	223,107	221,703	68	1,472	1,477	1,477	10,415	10,415
60	80.2	80.2	2,224	2,224	7,776	7,776	191,147	190,002	64	1,209	1,284	1,284	9,060	9,060
65	82.1	82.1	1,760	1,760	8,240	8,240	162,318	161,364	55	1,009	1,082	1,082	7,094	7,094
70	83.9	83.9	1,484	1,484	8,516	8,516	131,957	131,109	44	892	894	894	5,677	5,677
75	85.8	85.8	1,098	1,098	8,902	8,902	102,985	102,339	26	672	688	688	4,345	4,345
No end-of-life care costs														
45	74.3	74.0	3,565	3,793	6,435	6,207	277,564	271,734	87	1,705	1,802	1,796	14,029	14,852
50	76.4	76.1	3,199	3,379	6,801	6,621	249,332	244,596	73	1,564	1,738	1,730	12,538	13,166
55	78.3	78.1	2,748	2,928	7,252	7,072	219,998	215,879	70	1,420	1,506	1,479	11,099	11,829
60	80.0	79.9	2,353	2,461	7,647	7,539	189,650	186,904	65	1,188	1,263	1,238	9,458	9,912
65	82.0	81.9	1,854	1,934	8,146	8,066	161,276	159,330	58	1,002	1,081	1,086	7,504	7,757
70	83.8	83.8	1,564	1,614	8,436	8,386	131,183	129,769	42	889	863	862	6,014	6,233
75	85.8	85.8	1,144	1,181	8,856	8,819	102,646	101,650	25	673	683	688	4,518	4,647
BRCA-positive patients														
45	74.3	72.2	3,661	4,919	6,339	5,081	275,194	240,897	1,157	10,620	1,869	1,705	14,446	19,040
50	76.2	74.7	3,304	4,346	6,696	5,654	246,500	218,655	1,073	9,626	1,716	1,561	13,037	17,292
55	78.1	77.1	2,904	3,738	7,096	6,262	217,265	195,884	940	8,565	1,492	1,391	11,533	15,004
60	80.0	79.3	2,432	3,100	7,568	6,900	187,864	171,605	784	7,494	1,226	1,132	9,813	12,520
65	81.9	81.5	1,923	2,392	8,077	7,608	159,819	147,706	670	6,691	1,119	1,120	7,715	9,650
70	83.8	83.6	1,600	1,949	8,400	8,051	130,249	121,700	584	5,588	892	869	6,116	7,414
75	85.8	85.6	1,154	1,364	8,846	8,636	102,030	95,961	422	4,405	686	669	4,556	5,419
CPM health preference greater than surveillance														
45	74.3	74.0	3,565	3,793	6,435	6,207	277,564	271,734	87	1,705	1,802	1,796	14,029	14,852
50	76.4	76.1	3,199	3,379	6,801	6,621	249,332	244,596	73	1,564	1,738	1,730	12,538	13,166
55	78.3	78.1	2,748	2,928	7,252	7,072	219,998	215,879	70	1,420	1,506	1,479	11,099	11,829
60	80.0	79.9	2,353	2,461	7,647	7,539	189,650	186,904	65	1,188	1,263	1,238	9,458	9,912
65	82.0	81.9	1,854	1,934	8,146	8,066	161,276	159,330	58	1,002	1,081	1,086	7,504	7,757
70	83.8	83.8	1,564	1,614	8,436	8,386	131,183	129,769	42	889	863	862	6,014	6,233
75	85.8	85.8	1,144	1,181	8,856	8,819	102,646	101,650	25	673	683	688	4,518	4,647
CPM health preference less than surveillance														
45	74.3	74.0	3,565	3,793	6,435	6,207	277,564	271,734	87	1,705	1,802	1,796	14,029	14,852
50	76.4	76.1	3,199	3,379	6,801	6,621	249,332	244,596	73	1,564	1,738	1,730	12,538	13,166
55	78.3	78.1	2,748	2,928	7,252	7,072	219,998	215,879	70	1,420	1,506	1,479	11,099	11,829
60	80.0	79.9	2,353	2,461	7,647	7,539	189,650	186,904	65	1,188	1,263	1,238	9,458	9,912
65	82.0	81.9	1,854	1,934	8,146	8,066	161,276	159,330	58	1,002	1,081	1,086	7,504	7,757
70	83.8	83.8	1,564	1,614	8,436	8,386	131,183	129,769	42	889	863	862	6,014	6,233
75	85.8	85.8	1,144	1,181	8,856	8,819	102,646	101,650	25	673	683	688	4,518	4,647

Abbreviations: CPM, contralateral prophylactic mastectomy; Sur, routine surveillance.

health preference for CPM because they are no longer as fearful of developing a new CBC. Although the literature suggests that quality of life is similar in patients who undergo CPM or surveillance,^{35,36} we varied the utility weights of the CPM group to assess the impact of an individual's higher or lower health preference for the CPM health state

and found that results are sensitive to this assumption, highlighting the important role that individual health preferences play in the cost-effectiveness of prophylactic surgery.

Our study has some limitations. As is the case with modeling studies, our results depend on the data and assumptions used in the

model. Furthermore, modeling studies are limited in that they can capture only in broad strokes what happens in real life, because it is difficult to simplify the complexity inherent with modern day medical practice into a mathematical model. However, a randomized controlled trial to determine the cost and outcomes (QALYs) of CPM compared with surveillance would be infeasible, if not impossible, therefore a modeling approach may be the only realistic alternative. To minimize bias, only data from well-designed studies were used, and when available, an average of the model parameter was obtained from multiple sources. We did not consider costs generated to investigate a nonmalignant suspicious mass; it is likely that such false-positive diagnostic evaluations would occur more commonly in the routine surveillance group as a result of repeated screening mammograms. If we had included these costs, it would have further favored the cost-effectiveness of the CPM strategy. We did not take into account the potential benefits of detecting synchronous contralateral breast cancers in the breast specimens after CPM, because there is scant evidence regarding its prognostic implications. We also did not evaluate costs related to either immediate or delayed breast reconstruction. We can speculate that the inclusion of breast reconstruction into the model would increase both the total costs and the quality of life of patients in the CPM strategy; however, because our purpose was to purely compare two alternative CBC risk-management strategies, we opted not to do so, although we recognize that this represents a venue for further research. We also did not take into account complications related to the surgical event of the CPM occurring beyond initial treatment. These complications are usually minimal in the absence of breast reconstruction,^{12,41} and if they were to occur, they would likely occur during the initial treatment and be captured in our estimates obtained from the Nationwide Inpatient Sample database. We did not take into account indirect costs such as patient lost wages as a result of medical treatment after the index breast cancer. To have a complete appraisal from the societal perspective, these indirect costs would be necessary. Because the clinical outcomes were equivalent or favored CPM in all simulations, we hypothesize that lost wages would also be equivalent or favor CPM.

We did not separate patients by hormone receptor status, nor did we incorporate endocrine therapy; the use of transition probability estimates obtained from large studies encompassing heterogeneous populations and with high use of endocrine therapy would account for such hormone receptor variability and the effect of endocrine therapy on CBC risk. However, we do recognize that the use of endocrine therapy is far more complex; it is dependent on multiple factors such as patient acceptance, cost, adverse effects, discontinuation rate, and so on. Therefore, the exact impact that endocrine therapy might have on the cost-effectiveness of CPM versus surveillance represents fertile ground for further research in the field.

In conclusion, CPM seems to be a cost-effective strategy for the general population of patients with breast cancer who are younger than 70 years of age. CPM remains cost-effective at any age for patients whose health preference for CPM is higher than that of surveillance, whereas, conversely, surveillance dominates CPM if a patient's health preference for CPM is lower than that of surveillance. CPM is both less costly and provides more QALYs for high-risk patients (*BRCA* positive) of any age. Results should not be used to suggest that all patients should undergo a CPM, nor that CPM is superior to surveillance. The CPM discussion should be individualized to each patient, as this study highlights that the more cost-effective approach depends on patient preference for a particular health state.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception and design: All authors

Collection and assembly of data: Benjamin Zendejas, James P. Moriarty, Jamie O'Byrne, David R. Farley, Judy C. Boughey

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

1. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2009. *CA Cancer J Clin* 59:225-249, 2009
2. Tuttle TM, Habermann EB, Grund EH, et al: Increasing use of contralateral prophylactic mastectomy for breast cancer patients: A trend toward more aggressive surgical treatment. *J Clin Oncol* 25:5203-5209, 2007
3. Jones NB, Wilson J, Kotur L, et al: Contralateral prophylactic mastectomy for unilateral breast cancer: An increasing trend at a single institution. *Ann Surg Oncol* 16:2691-2696, 2009
4. Tuttle TM, Jarosek S, Habermann EB, et al: Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. *J Clin Oncol* 27:1362-1367, 2009
5. McLaughlin CC, Lillquist PP, Edge SB: Surveillance of prophylactic mastectomy: Trends in use from 1995 through 2005. *Cancer* 115:5404-5412, 2009
6. Rosen PP, Groshen S, Kinne DW, et al: Contralateral breast carcinoma: An assessment of risk and prognosis in stage I (T1N0M0) and stage II

(T1N1M0) patients with 20-year follow-up. *Surgery* 106:904-910, 1989

7. Peralta EA, Ellenhorn JD, Wagman LD, et al: Contralateral prophylactic mastectomy improves the outcome of selected patients undergoing mastectomy for breast cancer. *Am J Surg* 180:439-445, 2000

8. Herrinton LJ, Barlow WE, Yu O, et al: Efficacy of prophylactic mastectomy in women with unilateral breast cancer: A cancer research network project. *J Clin Oncol* 23:4275-4286, 2005

9. McDonnell SK, Schaid DJ, Myers JL, et al: Efficacy of contralateral prophylactic mastectomy in women with a personal and family history of breast cancer. *J Clin Oncol* 19:3938-3943, 2001

10. Lostumbo L, Carbine N, Wallace J, et al: Prophylactic mastectomy for the prevention of breast cancer. *Cochrane Database Syst Rev* 4:CD002748, 2004

11. Khatcheressian JL, Wolff AC, Smith TJ, et al: American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. *J Clin Oncol* 24:5091-5097, 2006

12. Goldflam K, Hunt KK, Gershengwald JE, et al: Contralateral prophylactic mastectomy: Predictors

of significant histologic findings. *Cancer* 101:1977-1986, 2004

13. Gao X, Fisher SG, Emami B: Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: A population-based study. *Int J Radiat Oncol Biol Phys* 56:1038-1045, 2003

14. Hankey BF, Curtis RE, Naughton MD, et al: A retrospective cohort analysis of second breast cancer risk for primary breast cancer patients with an assessment of the effect of radiation therapy. *J Natl Cancer Inst* 70:797-804, 1983

15. Schrag D, Kuntz KM, Garber JE, et al: Life expectancy gains from cancer prevention strategies for women with breast cancer and *BRCA1* or *BRCA2* mutations. *JAMA* 283:617-624, 2000

16. Hartmann LC, Sellers TA, Schaid DJ, et al: Efficacy of bilateral prophylactic mastectomy in *BRCA1* and *BRCA2* gene mutation carriers. *J Natl Cancer Inst* 93:1633-1637, 2001

17. Hemminki K, Ji J, Forsti A: Risks for familial and contralateral breast cancer interact multiplicatively and cause a high risk. *Cancer Res* 67:868-870, 2007

18. Metcalfe K, Lynch HT, Ghadirian P, et al: Contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers. *J Clin Oncol* 22:2328-2335, 2004

19. Surveillance, Epidemiology, and End Results (SEER): About SEER. National Cancer Institute. <http://www.seer.cancer.gov/about>
20. Arias E: United States Life Tables, 2004. National Vital Statistics Reports, vol 56, no 9. Hyattsville, MD, National Center for Health Statistics, 2007
21. Centers for Medicare and Medicaid Services: Medicare physician fee schedule, 2007. <http://www.cms.hhs.gov/PFSlookup/>
22. Healthcare Cost and Utilization Project: HCUP Nationwide Inpatient Sample (NIS): Healthcare Cost and Utilization Project (HCUP). 2000-2001. Rockville, MD, Agency for Healthcare Research and Quality. <http://www.hcup-us.ahrq.gov/nisoverview.jsp>
23. Berkowitz N, Gupta S, Silberman G: Estimates of the lifetime direct costs of treatment for metastatic breast cancer. *Value Health* 3:23-30, 2000
24. Lamerato L, Havstad S, Gandhi S, et al: Economic burden associated with breast cancer recurrence: Findings from a retrospective analysis of health system data. *Cancer* 106:1875-1882, 2006
25. Stokes ME, Thompson D, Montoya EL, et al: Ten-year survival and cost following breast cancer recurrence: Estimates from SEER-medicare data. *Value Health* 11:213-220, 2008
26. Kruse GB, Amonkar MM, Smith G, et al: Analysis of costs associated with administration of intravenous single-drug therapies in metastatic breast cancer in a U.S. population. *J Manag Care Pharm* 14:844-857, 2008
27. Anderson K, Jacobson JS, Heitjan DF, et al: Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. *Ann Intern Med* 144:397-406, 2006
28. Stout NK, Rosenberg MA, Trentham-Dietz A, et al: Retrospective cost-effectiveness analysis of screening mammography. *J Natl Cancer Inst* 98:774-782, 2006
29. Quan G, Pommier SJ, Pommier RF: Incidence and outcomes of contralateral breast cancers. *Am J Surg* 195:645-650, 2008
30. Schaapveld M, Visser O, Louwman WJ, et al: The impact of adjuvant therapy on contralateral breast cancer risk and the prognostic significance of contralateral breast cancer: A population based study in the Netherlands. *Breast Cancer Res Treat* 110:189-197, 2008
31. Naimark D, Bott M, Krahn M: The half-cycle correction explained: Two alternative pedagogical approaches. *Med Decis Making* 28:706-712, 2008
32. Weinstein MC, Siegel JE, Gold MR, et al: Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA* 276:1253-1258, 1996
33. Torrance GW: Measurement of health state utilities for economic appraisal. *J Health Econ* 5:1-30, 1986
34. Lee JM, McMahon PM, Kong CY, et al: Cost-effectiveness of breast MR imaging and screen-film mammography for screening BRCA1 gene mutation carriers. *Radiology* 254:793-800, 2010
35. Tercyak KP, Peshkin BN, Brogan BM, et al: Quality of life after contralateral prophylactic mastectomy in newly diagnosed high-risk breast cancer patients who underwent BRCA1/2 gene testing. *J Clin Oncol* 25:285-291, 2007
36. Geiger AM, West CN, Nekhlyudov L, et al: Contentment with quality of life among breast cancer survivors with and without contralateral prophylactic mastectomy. *J Clin Oncol* 24:1350-1356, 2006
37. International Monetary Fund: World Economic Outlook Database [database online]. Washington, DC, International Monetary Fund, 2010
38. World Health Organization: Macroeconomics and health: Investing in health for economic development: Report of the Commission on Macroeconomics and Health. Geneva, Switzerland, World Health Organization, 2001
39. Yi M, Meric-Bernstam F, Middleton LP, et al: Predictors of contralateral breast cancer in patients with unilateral breast cancer undergoing contralateral prophylactic mastectomy. *Cancer* 115:962-971, 2009
40. Schrag D, Kuntz KM, Garber JE, et al: Decision analysis: Effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 or BRCA2 mutations. *N Engl J Med* 336:1465-1471, 1997
41. Zion SM, Slezak JM, Sellers TA, et al: Reoperations after prophylactic mastectomy with or without implant reconstruction. *Cancer* 98:2152-2160, 2003