

# Cost-Effectiveness of Preventive Strategies for Women with a *BRCA1* or a *BRCA2* Mutation

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**Background:** For *BRCA1* or *BRCA2* mutation carriers, decision analysis indicates that prophylactic surgery or chemoprevention leads to better survival than surveillance alone.

**Objective:** To evaluate the cost-effectiveness of the preventive strategies that are available to unaffected women carrying a single *BRCA1* or *BRCA2* mutation with high cancer penetrance.

**Design:** Markov modeling with Monte Carlo simulations and probabilistic sensitivity analyses.

**Data Sources:** Breast and ovarian cancer incidence and mortality rates, preference ratings, and costs derived from the literature; the Surveillance, Epidemiology, and End Results (SEER) Program; and the Health Care Financing Administration (now the Centers for Medicare & Medicaid Services).

**Target Population:** Unaffected carriers of a single *BRCA1* or *BRCA2* mutation 35 to 50 years of age.

**Time Horizon:** Lifetime.

**Perspective:** Health policy, societal.

**Interventions:** Tamoxifen, oral contraceptives, bilateral salpingo-oophorectomy, mastectomy, both surgeries, or surveillance.

**Outcome Measures:** Cost-effectiveness.

**Results of Base-Case Analysis:** For mutation carriers 35 years of age, both surgeries (prophylactic bilateral mastectomy and oophorectomy) had an incremental cost-effectiveness ratio over oophorectomy alone of \$2352 per life-year for *BRCA1* and \$100 per life-year for *BRCA2*. With quality adjustment, oophorectomy dominated all other strategies for *BRCA1* and had an incremental cost-effectiveness ratio of \$2281 per life-year for *BRCA2*.

**Results of Sensitivity Analysis:** Older age at intervention increased the cost-effectiveness of prophylactic mastectomy for *BRCA1* mutation carriers to \$73 755 per life-year. Varying the penetrance, mortality rates, costs, discount rates, and preferences had minimal effects on outcomes.

**Limitations:** Results are dependent on the accuracy of model assumptions.

**Conclusion:** On the basis of this model, the most cost-effective strategies for *BRCA* mutation carriers, with and without quality adjustment, were oophorectomy alone and oophorectomy and mastectomy, respectively.

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Germline mutations account for 5% to 10% of breast cancer diagnosed in the United States each year (1). Because women who develop cancer associated with such mutations do so at a relatively young age, these mutations account for a disproportionate share of life-years lost due to cancer. Genetic testing is expensive, but so is cancer. Hence, cost-effective policies on testing and preventive treatment options may save up to \$800 million of the more than \$8 billion or more spent each year on breast cancer diagnosis, prevention, and treatment (2–4).

In a recent decision analysis of preventive strategies, we reported that prophylactic surgery or chemoprevention could lead to better survival and quality-adjusted survival than surveillance alone for women with a positive test result for *BRCA1* or *BRCA2* mutations (5). We showed that the survival benefit for women who had prophylactic mastectomy with bilateral oophorectomy at 30 years of age was 4.9 years, but it increased to 7.8 years if the penetrance rates of breast and ovarian cancer were 85% and 63%, respectively. These results are similar to those found in other decision analyses (6–10), although the outcomes for women treated with prophylactic surgery, especially prophylactic oophorectomy, have improved in more recent observational data (11–13).

Recently, King and colleagues (13) published findings on breast and ovarian cancer penetrance in a cohort of

unaffected women who received a positive test result for a specific *BRCA1* or *BRCA2* mutation. To assist policymakers and those who pay for medical care, using a societal perspective, we have incorporated these findings (6) into our mathematical model to estimate the cost-effectiveness of each strategy given a *BRCA1* or a *BRCA2* mutation. In light of questions raised about the penetrance data (14–16) and other factors, we have also conducted sensitivity analyses in which we varied our assumptions about mutation penetrance; cancer mortality; and the timing, efficacy, costs, and preference ratings of preventive interventions to identify threshold values for these strategies.

## METHODS

We developed a Markov process (17) and used 25 000 Monte Carlo simulations with TreeAge DATA Pro soft-

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**Context**

Recent research has provided more precise estimates of the age-specific incidence of ovarian and breast cancer in carriers of *BRCA* mutations. These data will help define the value of prophylactic surgery for these women.

**Content**

For *BRCA2* carriers, the authors' decision model shows that combined prophylactic surgery (mastectomy and bilateral salpingo-oophorectomy) was very cost-effective relative to oophorectomy alone. Both strategies dominated (were less costly and were more effective) surveillance, prophylactic mastectomy alone, or chemoprevention. For *BRCA1* carriers, oophorectomy dominated all other strategies.

**Limitations**

The model uses observational study data and expert opinion.

**Implications**

Oophorectomy alone or in combination with mastectomy is the most cost-effective strategy for *BRCA* mutation carriers.

—The Editors

ware (TreeAge Software Inc., Williamstown, Massachusetts) to estimate the cost-effectiveness of the following preventive strategies for women with a positive test result for *BRCA1* or *BRCA2* mutations: chemoprevention (tamoxifen for breast cancer and oral contraceptives for ovarian cancer), prophylactic surgery (bilateral mastectomy for breast cancer and bilateral salpingo-oophorectomy for ovarian cancer; oophorectomy also reduces the risk for breast cancer), or both surgical procedures for breast and ovarian cancer, and surveillance alone. For surveillance, we assumed that women with a positive test result would follow the guidelines outlined by Burke and colleagues (18) and the National Comprehensive Cancer Network (19), which include annual mammography; breast ultrasonography, if necessary; clinical breast examinations; and semi-annual gynecology examinations, including pelvic examinations, ultrasonography, and CA-125 studies.

We focused on 8 health outcomes: good health; death; breast cancer; ovarian cancer; both breast cancer and ovarian cancer; and side effects of oral contraceptives and tamoxifen, such as cataracts, endometrial cancer, and thrombophlebitis or pulmonary emboli (Table 1). We used 25 000 simulations for our base case, in which women initiate their preventive strategy at 35 years of age, with up to 70 years of follow-up (Markov cycles). For each year and

**Table 1. Incidence, Preventive Strategy, and Mortality Assumptions Used in the Markov Model\***

Variable	Value
<b>Health states per 100 persons per y ± SE, n</b>	
Breast cancer (6)	
<i>BRCA1</i> mutation carrier	3.32 ± 0.63
<i>BRCA2</i> mutation carrier	3.79 ± 1.07
Ovarian cancer (6)	
<i>BRCA1</i> mutation carrier	1.55 ± 0.304
<i>BRCA2</i> mutation carrier	0.523 ± 0.031
Endometrial cancer due to tamoxifen (14)	0.401 ± 0.019
Pulmonary embolism due to tamoxifen (14)	0.320 ± 0.180
Cataracts due to tamoxifen (14)	0.110 ± 0.050
<b>Preventive strategies ± SE, %</b>	
Breast cancer risk reduction due to:	
Prophylactic bilateral mastectomy (20)	90 ± 0.05
Mastectomy and oophorectomy (20, 21)	95 ± 0.05
Tamoxifen (14, 22)	49 ± 0.07
Oophorectomy before age 50 years (21)	45 ± 0.1
Ovarian cancer risk reduction due to:	
Oophorectomy (TreeAge DATA Prot)	96 ± 0.03
Oral contraceptives (23)	54 ± 0.11
<b>Mortality (15)</b>	
Breast cancer	1 – SEER survival rates ≤ 0–20 y after diagnosis; U.S. population mortality rates thereafter (15)
Ovarian cancer	1 – SEER survival rates ≤ 0–20 y after diagnosis; U.S. population mortality rates thereafter (15)
Endometrial cancer (14)	1 – SEER survival rates ≤ 5 y after diagnosis; U.S. population rates > 5 y (15) for 15% of mixed müllerian tumors 0–5 y after diagnosis (24); U.S. population rates (15)
Pulmonary embolism (14)	3% in first year; U.S. population rates after 1 year (14, 15)
Cataracts (14)	U.S. population rates (15)

\* Values in parentheses are reference numbers. SEER = Surveillance, Epidemiology, and End Results.

† TreeAge Software, Inc., Williamstown, Massachusetts.

each strategy, we calculated the age-dependent probabilities of developing breast cancer, developing ovarian cancer, developing side effects, dying of breast or ovarian cancer, dying of any cause, or remaining well. The **Figure** depicts the preventive strategies, the health outcomes, and further health outcomes included in the model. For our base case, we ranked our preventive strategies by cost and determined which strategy had the most favorable cost-effectiveness ratio with and without quality adjustment.

**Health Parameters**

The model used King and colleagues’ estimates of the cumulative incidence (penetrance) of breast cancer and ovarian cancer among *BRCA1*- and *BRCA2*-positive women (13) in each decade of age up to 100 years. We converted these 10-year risks to annual conditional probabilities of cancer by assuming constant instantaneous rates of disease per year within each decade. We assumed that the risks for developing the 2 types of cancer were independent. Therefore, among *BRCA1*- or *BRCA2*-positive women, those with breast cancer had the same conditional probability of developing ovarian cancer as those who were well.

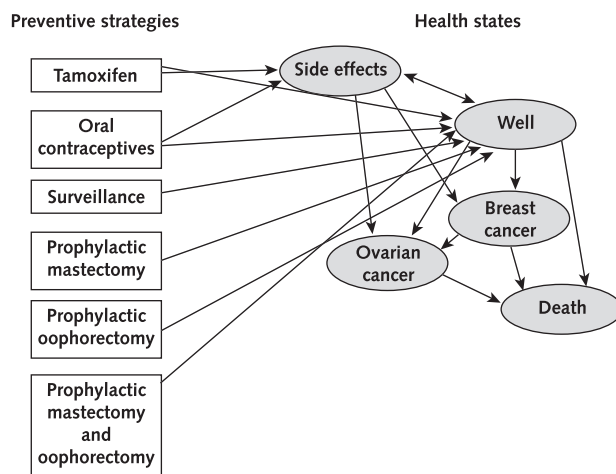
For patients who developed breast cancer, we calculated the annual risks for death, ovarian cancer, or survival with breast cancer. We took into account both the age when the patient received the diagnosis and the time from diagnosis.

Because intensive surveillance may influence stage at diagnosis, we assumed that *BRCA1*- or *BRCA2*-positive women, given a choice of preventive measures at 35 years of age and subsequently receiving a diagnosis of breast cancer, would be similar in stage distribution to the participants in the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 Study, known as the Breast Cancer Prevention Trial (BCPT) (25). Of these participants, 70% had localized (node-negative) and 30% had regional (node-positive) disease (25).

We assumed that *BRCA1*- or *BRCA2*-positive women who developed cancer would have the same conditional probability of death as women with cancer in the general population. Therefore, we used the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program data issued in 2001 (20) to calculate the probabilities of death. We did not adjust for screening for ovarian cancer because screening does not seem to alter the prognosis of this type of cancer (26, 27).

We based our estimates of the health effects of preventive strategies on findings that bilateral prophylactic oophorectomy and salpingo-oophorectomy may reduce the risk for ovarian cancer and breast cancer by 96% (11, 23, 28) and 53% (11), respectively, among *BRCA1*- and *BRCA2*-positive women. Other recent studies suggest that bilateral prophylactic mastectomy may reduce the risk for breast cancer by 90% (12, 21, 29), tamoxifen (taken for 5 years) may reduce the risk for breast cancer by 49% (25,

**Figure. Preventive strategies and health states (outcomes) used in the Markov model and probabilistic sensitivity analysis.**



30), and oral contraceptives may reduce the risk for ovarian cancer by 54% (31, 32). For our base case, we assumed that the risk reductions associated with these strategies lasted indefinitely.

We assumed that women 35 years of age who were given estrogen replacement therapy until 50 years of age after prophylactic oophorectomy would not have an increased risk for breast cancer more than that conferred by *BRCA1* or *BRCA2* (8, 33). We also assumed that they would have the same risk for cardiovascular disease and osteoporosis as that of the general population. We calculated the incremental mean years of survival that each preventive measure would yield by subtracting that value from the mean life expectancy associated with surveillance.

We assumed that women who experienced serious side effects from tamoxifen or oral contraceptives would discontinue those treatments and thereafter use only surveillance as a strategy.

**Cost Parameters**

We included the costs of genetic testing and screening in our model (34). We obtained age-stratified data on cancer care costs from Kaiser Permanente (Table 2) (35). We based our estimates of the costs of treating complications, such as endometrial cancer, thrombophlebitis with pulmonary embolism, and cataracts (Table 2), on Medicare payments from the Health Care Financing Administration (now the Centers for Medicare & Medicaid Services) (38, 40). We based our estimates of the costs of care for those dying with and without cancer on analyses of these data by Riley and colleagues (36) and Lubitz and Riley (37). We obtained drug cost data from the 2004 Drug Topics Red Book (39). We adjusted all costs for increases in the medical care component of the Consumer Price Index (4) and provided the values in 2004 U.S. dollars.

Table 2. Medical Costs Used in the Markov Model\*

Variable (Reference)	Costs, \$
First year after diagnosis (35)	26 412† (breast cancer‡); 55 323† (ovarian cancer)
Yearly costs (35)	6784† (breast cancer‡); 10 055† (ovarian cancer)
Terminal care costs, last year of life (35–37)	38 932† (breast cancer‡); 38 743† (ovarian cancer)
Surveillance (per NCCN guidelines) (18, 19)	3601 (without breast or ovarian cancer†)
Terminal care costs, last year of life (35–37)	28 787 (without breast or ovarian cancer†)
Other medical costs†	
Endometrial cancer (38)†	
Preoperative evaluation consultation	157
Pathologist for biopsy of endometrium	49
Ultrasonography	115
Radiologist for reading ultrasound	41
DRG 355 (hysterectomy for malignant condition)	3814
Physician payment for surgery	1006
Pathologist payment (in-hospital)	97
Total	5279
Pulmonary emboli (38)†	
Inpatient	
DRG 128 (pulmonary emboli)	3311
Physician admission visit	131
Physician daily visits (6 d)	370
V/Q scan, radiologist	63
Outpatient anticoagulation for 3 mo	
Warfarin (100 five-mg pills) (39)	68
Eight protime tests	131
Eight physician visits	323
Total	4396§
Cataract surgery (38)†	
DRG 39 (cataract surgery)	2589
Physician payment for surgery	800
Total	3389
Genetic testing and counseling (30)	385 (testing); 230 (counseling)
Preventive strategies†	
Tamoxifen cost per year (for 5 y) (39)	623
Prophylactic mastectomy (38)	11 303
Prophylactic salpingo-oophorectomy (38)	4622
Both prophylactic mastectomy and salpingo-oophorectomy (38)	15 925
Oral contraceptives (39)	379
Prophylactic salpingo-oophorectomy and tamoxifen (cost per year for 5 y) (39)	7737

\* The discount rate (range) was 3% (0%–5%). DRG = diagnosis-related group; NCCN = National Comprehensive Cancer Network; V/Q = ventilation–perfusion.

† Adjusted by the Medical Consumer Price Index into 2004 U.S. dollars (4).

‡ Yearly costs for patients with breast cancer apply to years 2 to 17 after diagnosis. Cost for years >17 are the same as those for healthy women.

§ Value does not equal the sum of the rows because of rounding.

We did not determine indirect costs, such as those due to time off from work, travel, and other out-of-pocket expenses, and we assumed them to be inconsequential compared with direct medical costs (41).

### Quality-of-Life Adjustment

We used preference ratings of cancer treatment–related and preventive treatment–related states obtained from our study (24, 42) by using time-tradeoff ratings among women 33 to 50 years of age with a family history of breast cancer (at least 1 first-degree relative diagnosed before 50 years of age) or with a personal history of several breast biopsies (Table 3). We obtained preference ratings of the side effects of tamoxifen from the literature. In our computer model, we adjusted the incremental life expectancy attributed to each preventive measure by its preference rating on a 0- to 1-point scale to derive quality-adjusted life-years (QALYs). We compared the QALYs of chemoprevention and surgery with those of surveillance to

derive incremental QALYs. We used the preference rating for chemoprevention as the quality adjustment factor for both tamoxifen and oral contraception. To estimate QALYs for the 2 cancer states, we used a weighted average of the ratings of nonmetastatic disease and metastatic disease on the assumption that the proportion of patients with cancer who currently have metastatic disease equals the proportion of patients expected to die in the subsequent 3 years (46). We assumed that women who entered a new health state, such as breast or ovarian cancer, would assume the utility of that health state.

### Discounting

We used a discount rate of 3% (range, 0% to 5%).

### Special Complications of Chemoprevention

Into our model, we incorporated only statistically significant BCPT data, such as the risks for cataracts, thrombophlebitis, pulmonary emboli, and endometrial cancer

(25). In that trial, these risks were associated with tamoxifen only among women older than 50 years of age except for risk for cataracts (25). We obtained risks for death due to pulmonary embolus from the literature and risks for death due to endometrial cancer from SEER data (20, 44). On the basis of a recent BCPT report (47), we assumed that 15% of endometrial cancer would be mixed müllerian tumors and the remaining 85% would be low-grade endometrial cancer. The expected survival of patients with malignant mixed müllerian tumors is less than 5 years (48, 49). For oral contraceptives, we assumed the risk for thrombophlebitis and pulmonary emboli to be similar to that of tamoxifen (50). We assumed that the costs of these complications beyond the first year were the same as those among other high-risk women who had not taken tamoxifen.

### Sensitivity Analysis

We conducted sensitivity analyses of testing for mutations and implementing the preventive strategies at 40 years, 45 years, or 50 years of age. The efficacy of tamoxifen and newer selective estrogen receptor modulators among premenopausal *BRCA1*- or *BRCA2*-positive women is unknown. Many, although not all, patients with breast cancer with *BRCA1* mutations have hormone receptor-negative tumors (51–54). Most patients with breast cancer with *BRCA2* mutations have estrogen receptor-positive tumors (55). Because BCPT found that tamoxifen prevented hormone receptor-positive but not hormone receptor-negative cancer, we performed additional sensitivity analyses, assuming that the reduction in breast cancer risk among *BRCA1*- or *BRCA2*-positive women who take tamoxifen is only 25% or 15% rather than 49% (Table 4) (25, 56–59). We also varied mortality rates, discount rates, costs, and preference ratings.

The true penetrance of *BRCA1* and *BRCA2* is uncertain. We therefore conducted sensitivity analyses by decreasing the breast cancer incidence rates to 50%, 25%, and 12.5% (similar to those of the healthy population). We decreased the ovarian cancer incidence rate to 16%.

### Critique of Data Quality

We based our assumptions in the model on observational study results. Although chemoprevention and screening modality trials are being conducted, randomized trials comparing surgical interventions with surveillance are unlikely. Until the trial data are available, we must rely on observational studies with assumptions based on expert opinion and the available literature. Our cost estimates also rely on observational studies, such as one that compares the costs incurred by patients with ovarian cancer and patients with breast cancer with those incurred by controls in a health maintenance organization (35). However, the literature on these costs among women of similar age is sparse and is somewhat dated. Attributable costs for breast cancer used in our model are similar to those found in a recent cost analysis of a similar population (60). We gathered

**Table 3. Preference Ratings Used for Quality Adjustment**

Health States (Reference)	Mean (SD) Preference Ratings
Perfect health*	1.00
Cancer states among high-risk women* (24)	
Breast cancer	0.77 (0.22)
Ovarian cancer	0.65 (0.21)
Preventive measures at age of testing* (24)	
Prophylactic mastectomy	0.76 (0.26)
Chemoprevention	0.81 (0.25)
Prophylactic bilateral salpingo-oophorectomy	0.82 (0.27)
Both surgeries	0.73 (0.25)
Well with positive <i>BRCA1</i> or <i>BRCA2</i> test result* (24)	0.76 (0.29)
Other health states associated with tamoxifen†	
Endometrial cancer (43)	0.68
Pulmonary emboli (44)	0.50
Cataract surgery (45)	0.68
Death	0.00

\* Preferences are based on responses to a time-tradeoff questionnaire using a 0- to 1.00-point scale (24).

† Preferences are from the literature and are based on the time spent in that health state: 5 y for endometrial cancer and 1 y for pulmonary emboli and cataract surgery.

quality-of-life estimates from the literature and from the Harvard cost-effectiveness registry (42).

We used SEER data to assess mortality rates for cancer. A recent study suggested that among women with breast cancer who had breast-conserving surgery, *BRCA1* mutation carriers had higher mortality rates than other women. However, the *BRCA1* carriers were less likely to have received adjuvant chemotherapy than the other women (61, 62). Most other studies have not suggested that mortality is higher for mutation carriers than for other women with breast cancer. The higher the mortality assumed to be associated with *BRCA1* or *BRCA2* mutations given surveillance alone, the greater are the survival and cost-effectiveness benefits of preventive interventions (5). We used the most conservative estimates of each parameter so that our model would, if biased, favor surveillance over other preventive interventions.

### Model Output

On the basis of these data, the model generated estimates of the health care costs in U.S. dollars and the survival and quality-adjusted survival in life-years associated with each strategy; the incremental costs of each strategy compared with the least costly strategy; and the incremental cost-effectiveness of each strategy in U.S. dollars per life-year saved or QALY compared with the least costly strategy (incremental cost-effectiveness ratio). The model labeled the strategy that was least costly and yielded the longest survival as the dominant strategy.

### Role of the Funding Source

This analysis was supported by a research scholar grant from the American Cancer Society. The funding source had no role in the design, conduct, or reporting of the study or in the decision to submit the paper for publication.

**Table 4. Cost-Effectiveness of Preventive Strategies for Women with *BRCA1* and *BRCA2* Mutations\***

Strategy	Without Quality Adjustment				
	Cost (SD), \$†	Incremental Cost, \$	Life-Years (SD)	Incremental Life-Years Saved	Incremental Cost-Effectiveness, \$/life-year saved
<b><i>BRCA1</i></b>					
Bilateral salpingo-oophorectomy	119 058 (3119)	–	22.88 (0.59)	–	–
Mastectomy with bilateral salpingo-oophorectomy	120 869 (3129)	1811	23.65 (0.63)	0.77	2352
Oral contraceptives	130 205 (3406)	9336	21.57 (0.53)	–2.08	Dominated
Tamoxifen	135 130 (3709)	14 261	21.55 (0.54)	–2.10	Dominated
Surveillance	136 339 (3663)	15 470	21.07 (0.51)	–2.58	Dominated
Mastectomy	144 525 (4143)	23 656	22.06 (0.56)	–1.59	Dominated
<b><i>BRCA2</i></b>					
Bilateral salpingo-oophorectomy	116 186 (2749)	–	22.90 (0.59)	–	–
Mastectomy with bilateral salpingo-oophorectomy	116 277 (2515)	91	23.81 (0.63)	0.91	100
Tamoxifen	121 735 (2977)	5458	22.29 (0.56)	–1.52	Dominated
Oral contraceptives	122 430 (2915)	6153	21.89 (0.54)	–1.92	Dominated
Surveillance	124 430 (3057)	8153	21.64 (0.53)	–2.17	Dominated
Mastectomy	125 597 (3140)	9320	23.01 (0.60)	–0.80	Dominated

\* Based on 25 000 Monte Carlo simulations. QALY = quality-adjusted life-year.  
† Discount rate = 3%.

## RESULTS

Table 5 shows the lifetime breast and ovarian cancer incidence estimates generated by our model for each preventive strategy among women with a *BRCA1* or a *BRCA2* mutation. Table 4 presents the results of our cost-effectiveness analyses for quality-adjusted and unadjusted survival of preventive strategies initiated at age 35 years. The preferred strategy depended on whether the model included quality adjustment. For *BRCA1* mutation carriers, salpingo-oophorectomy and combined prophylactic mastectomy and salpingo-oophorectomy dominated the other strategies, with the combined strategy having an incremental cost-effectiveness ratio of \$2352 per life-year saved compared with oophorectomy alone. With quality adjustment, bilateral salpingo-oophorectomy dominated all other strategies. Although these strategies remained optimal for cost-effectiveness even if initiated at older ages (Table 6), delaying the strategy initiation to age 50 years increased the unadjusted incremental cost-effectiveness ratio of prophylactic mastectomy and salpingo-oophorectomy to \$73 755 per life-year saved.

The same procedures were preferred in the analyses of *BRCA2* mutation carriers. For *BRCA2* carriers 35 years of age, the combined surgery dominated all strategies except oophorectomy and had an incremental cost-effectiveness ratio of only \$100 per life-year saved with respect to oophorectomy. In quality-adjusted analysis, the result was the same, except that the incremental cost-effectiveness ratio was \$2281 per QALY. The same 2 strategies remained optimal or cost-effective even when they were initiated at older ages (Table 6).

Table 7 shows the effects of assuming lower penetrance of breast cancer in mutation carriers. Even when cancer risk decreased from 85% to 12.5%, the same strat-

egies remained cost-effective or cost-saving. We also analyzed the effects of assuming that tamoxifen would reduce breast cancer risk less than observed in BCPT, but because the tamoxifen strategy was dominated by the other strategies in the base case, it remained dominated. Similarly, when we used the preference ratings of women without increased cancer risk between 33 and 50 years of age instead of the preferences of women at higher-than-average risk, the most cost-effective strategies remained the same for women with either a *BRCA1* or a *BRCA2* mutation (data not shown). Increasing the mortality rates and costs and changing the discount rate had little effect on the incremental cost-effectiveness ratios (data not shown).

## DISCUSSION

On the basis of our decision-analysis model, the most cost-effective strategies with and without quality adjustment for women with positive test results for either a *BRCA1* or a *BRCA2* mutation were prophylactic bilateral salpingo-oophorectomy and prophylactic oophorectomy and mastectomy, respectively. Cost-effectiveness varied with age; younger women seemed likely to benefit the most from these interventions. Cost-effectiveness was also associated with penetrance (lifetime risk for cancer). When we reduced the penetrance of the mutations to 12.5%, which is equivalent to average risk for breast cancer among women in the United States, the 2 surgeries were not cost-effective for women with either mutation. However, even at that low level of penetrance, with quality adjustment, oophorectomy remained cost-effective. Increasing mortality rate and treatment costs and changing the discount rate did not affect the ranking of the strategies.

With quality adjustment, strategies involving prophyl-

**Table 4—Continued**

With Quality Adjustment				
Cost (SD), \$†	Incremental Cost, \$	QALYs (SD)	Incremental QALYs	Incremental Quality-Adjusted Cost-Effectiveness, \$/QALY
118 605 (3093)	–	18.39 (2.69)	–	–
120 533 (3167)	1928	17.44 (4.22)	–0.95	Dominated
129 908 (3452)	11 303	16.84 (1.39)	–1.55	Dominated
134 796 (3698)	16 191	16.75 (2.11)	–1.64	Dominated
135 858 (3712)	17 253	15.64 (1.43)	–2.75	Dominated
144 295 (3993)	25 690	16.44 (2.92)	–1.95	Dominated
116 213 (2665)	–	17.69 (3.62)	–	–
117 741 (2820)	1528	18.36 (2.55)	0.67	2281
121 387 (2672)	3646	17.74 (2.50)	–0.62	Dominated
122 153 (2672)	4412	17.32 (1.40)	–1.04	Dominated
124 016 (3244)	6275	16.42 (1.22)	–1.94	Dominated
125 477 (2780)	7736	17.53 (3.41)	–0.83	Dominated

lactic mastectomy were not cost-effective because despite its survival benefits, women are reluctant to have prophylactic mastectomy. These findings are consistent with those of other studies among women seen in high-risk clinics (63–66).

We developed our cost-effectiveness estimates to help health policymakers and payers compare interventions that are intended to prevent cancer among those who have inherited a confirmed cancer-related germline mutation of either *BRCA1* or *BRCA2* (22). Through sensitivity analysis, we have attempted to identify the factors that influence the cost-effectiveness of these strategies.

Using the BCPT results for tamoxifen chemoprevention of breast cancer according to Gail model risks, we previously determined that populations with a high risk for breast cancer have more to gain from screening and prevention than other populations (67). Other studies have had similar findings in preventive procedures for other conditions (cholesterol screening, Papanicolaou smear testing, and colonoscopy) (22, 68, 69). Using the mutation penetrance figures reported for unaffected populations (67), we also found that the level of cancer risk influenced the cost-effectiveness estimates, but most treatments remained cost-saving or cost-effective even given low mutation penetrance.

Our study indicates the importance of using preference ratings for cost-effectiveness analyses. Individual ratings of quality of life in the health states associated with cancer and prevention vary. For many women, the impact of surgical disfigurement may outweigh the benefit of cancer prevention. In a previous study, we found that women who were at average risk for breast cancer were less willing than high-risk women to trade time for quality of life but had generally similar ratings of cancer relative to preventive

strategies (24). Of course, the validity of these results depends on the accuracy of the assumptions used in our model.

The effects of tamoxifen and other serum estrogen receptor modulators, aromatase inhibitors, and anti-inflammatory agents, alone or in conjunction with prophylactic

**Table 5. Markov Model Estimates of the Lifetime Risks for Breast and Ovarian Cancer Associated with Each Preventive Strategy**

Preventive Strategies	Lifetime Risks, %	
	<i>BRCA1</i>	<i>BRCA2</i>
<b>Surveillance</b>		
Breast cancer	62	76
Ovarian cancer	52	23
<b>Tamoxifen</b>		
Breast cancer	43	59
Ovarian cancer	49	23
<b>Oral contraceptives</b>		
Breast cancer	65	79
Ovarian cancer	33	12
<b>Prophylactic salpingo-oophorectomy</b>		
Breast cancer	53	61
Ovarian cancer	13	6
<b>Prophylactic mastectomy</b>		
Breast cancer	23	28
Ovarian cancer	55	24
<b>Prophylactic mastectomy and salpingo-oophorectomy</b>		
Breast cancer	22	23
Ovarian cancer	12	4

**Table 6. Sensitivity Analysis of Age at Initiation of Preventive Strategies\***

Mutation	Age, y	Preferred Strategy	ICER, \$/life-year	Preferred Strategy	ICER, \$/QALY
<i>BRCA1</i>	35	Prophylactic mastectomy and oophorectomy	2352	Prophylactic salpingo-oophorectomy	Dominates‡
	40	Prophylactic mastectomy and oophorectomy	11 673	Prophylactic salpingo-oophorectomy	Dominates‡
	45	Prophylactic mastectomy and oophorectomy	31 336	Prophylactic salpingo-oophorectomy	Dominates‡
	50	Prophylactic mastectomy and oophorectomy	73 755	Prophylactic salpingo-oophorectomy	Dominates‡
<i>BRCA2</i>	35	Prophylactic mastectomy and oophorectomy	100	Prophylactic salpingo-oophorectomy	2281§
	40	Prophylactic mastectomy and oophorectomy	6918	Prophylactic salpingo-oophorectomy	Dominates‡
	45	Prophylactic mastectomy and oophorectomy	20 704	Prophylactic salpingo-oophorectomy	Dominates‡
	50	Prophylactic mastectomy and oophorectomy	34 964	Prophylactic salpingo-oophorectomy	Dominates‡

\* ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.  
 † Compared with prophylactic salpingo-oophorectomy.  
 ‡ Has less incremental cost and more incremental effectiveness than all other strategies.  
 § Compared with prophylactic mastectomy and oophorectomy.

oophorectomy, on cancer risk in women with *BRCA1* and *BRCA2* mutations are not yet known, but these agents may offer such women additional preventive options, especially if combined with oophorectomy. More effort should be devoted to developing clinical trials among these high-risk women. Observational studies have reported that tamoxifen combined with prophylactic oophorectomy reduces cancer risk dramatically (70), but these results await confirmation. Oral contraceptives also seem to reduce ovarian cancer risk and, in a recent study, did not seem to increase the risk for breast cancer (31, 32, 71).

In our study, we found that prophylactic oophorectomy was cost-saving (dominant) for *BRCA1* mutation carriers and was cost-effective for *BRCA2* mutation carriers when adjusted for the preferences of high-risk women. However, even among high-risk women, preferences are not uniform. The availability of options for the primary prevention of breast cancer is a relatively recent development. Our analyses indicate that any primary prevention strategy that we studied would be cost-effective or cost-saving compared with surveillance in the setting of genetic high risk (Table 4). We therefore recommend that policymakers support primary prevention in this setting.

Research on the genetic mutations that increase risk for breast and ovarian cancer and research on preventive

interventions have made enormous strides in the past decade, but many questions remain unanswered. For example, little is known about the risks of hormone replacement therapy for women who have prophylactic oophorectomy before 50 years of age, although 2 studies have not found adverse effects among women in this age group (8, 33). Chemopreventive agents, alone or in conjunction with prophylactic oophorectomy, need to be studied. Will they be safe and effective, and will their efficacy differ among *BRCA1* and *BRCA2* mutation carriers?

We believe that our study is the first to analyze the cost-effectiveness of preventive strategies for women with *BRCA1* and *BRCA2* mutations separately. We found that mastectomy had a more favorable cost-effectiveness profile in *BRCA2* carriers than in *BRCA1* carriers. With more specific knowledge about cancer-related mutations, we can help patients and physicians choose the most appropriate preventive strategies and enable policymakers to make the best use of health care resources.

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**Table 7. Sensitivity Analysis of Penetrance Rates for Breast Cancer and Incremental Cost-Effectiveness among Mutation Carriers\***

Mutation	Penetrance, %	Preferred Strategy	ICER, \$/life-year	Preferred Strategy	ICER, \$/QALY
<i>BRCA1</i>	85	Prophylactic mastectomy and oophorectomy	2352	Prophylactic salpingo-oophorectomy	Dominates‡
	50	Prophylactic mastectomy and oophorectomy	11 792	Prophylactic salpingo-oophorectomy	Dominates‡
	25	Prophylactic mastectomy and oophorectomy	25 157	Prophylactic salpingo-oophorectomy	Dominates‡
	12.5	Prophylactic mastectomy and oophorectomy	59 409	Prophylactic salpingo-oophorectomy	Dominates‡
<i>BRCA2</i>	85	Prophylactic mastectomy and oophorectomy	100	Prophylactic salpingo-oophorectomy	2281§
	50	Prophylactic mastectomy and oophorectomy	6108	Prophylactic salpingo-oophorectomy	Dominates‡
	25	Prophylactic mastectomy and oophorectomy	21 006	Prophylactic salpingo-oophorectomy	Dominates‡
	12.5	Prophylactic mastectomy and oophorectomy	51 260	Prophylactic salpingo-oophorectomy	Dominates‡

\* ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.  
 † Compared with prophylactic salpingo-oophorectomy.  
 ‡ Has less incremental cost and more incremental effectiveness than all other strategies.  
 § Compared with prophylactic mastectomy and oophorectomy.

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