Life Expectancy Gains From Cancer Prevention Strategies for Women With Breast Cancer and BRCA1 or BRCA2 Mutations

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INHERITED MUTATIONS IN THE BRCA1 and BRCA2 genes predispose women to both breast and ovarian cancers, often at young ages. Furthermore, women with breast cancer who carry a BRCA1 or BRCA2 (BRCA1/2) mutation develop second contralateral breast cancers and ovarian cancers at higher rates than do women with breast cancer who lack a germline BRCA1/2 mutation. For young women with breast cancer and high-penetration BRCA1/2 mutations, the lifetime probability of developing a contralateral breast cancer may be as high as 65%, and the probability of developing ovarian cancer may exceed 40%.3-5 In comparison, young women with breast cancer who lack these mutations face approximate lifetime risks of 10% for contralateral breast cancer and 2% for ovarian cancer.3-7

While intensified screening may identify cancers at a favorable stage, it cannot prevent them. Therefore, women with BRCA-associated breast cancer may consider prevention strategies such as tamoxifen, prophylactic contralateral mastectomy (PCM), or prophylactic oophorectomy (PO) to reduce their risk for second cancers. Although the efficacy of these approaches for BRCA1/2 mutation carriers is not certain, interim estimates can be extrapolated from stud-

Context Women with BRCA1- or BRCA2-associated breast cancer are at increased risk for contralateral breast cancer and ovarian cancer and therefore may consider secondary cancer prevention strategies, such as prophylactic surgery and tamoxifen therapy. It is not proven to what extent these strategies reduce risk of second cancers in such patients.

Objective To examine the effect of tamoxifen therapy, bilateral prophylactic oophorectomy (PO), prophylactic contralateral mastectomy (PCM), and combinations of these strategies on life expectancy for women with unilateral breast cancer and a BRCA1 or BRCA2 gene mutation.

Design and Setting Decision analysis using a Markov model. Probabilities for developing contralateral breast cancer and ovarian cancer, dying from these cancers, dying from primary breast cancer, and the reduction in cancer incidence and mortality due to prophylactic surgeries and/or tamoxifen were estimated from published studies.

Participants Hypothetical breast cancer patients with BRCA1 or BRCA2 mutations facing decisions about secondary cancer prevention strategies.

Interventions Seven strategies, including 5 years of tamoxifen use, PO, PCM, and combinations of these strategies, compared with careful surveillance.

Main Outcome Measures Total and incremental life expectancy (LE) with each intervention strategy.

Results Depending on the assumed penetrance of the BRCA mutation, compared with surveillance alone, 30-year-old early-stage breast cancer patients with BRCA mutations gain in LE 0.4 to 1.3 years from tamoxifen therapy, 0.2 to 1.8 years from PO, and 0.6 to 2.1 years from PCM. The magnitude of these gains is least for women with low-penetration mutations (assumed contralateral breast cancer risk of 24% and ovarian cancer risk of 6%) and greatest for those with high-penetration mutations (assumed contralateral breast cancer risk of 65% and ovarian cancer risk of 40%). Older age and poorer prognosis from primary breast cancer further attenuate these gains.

Conclusions Interventions to prevent second cancers, particularly PCM, may offer substantial LE gain for young women with BRCA-associated early-stage breast cancer. Estimates of LE gain may help women and their physicians consider the uncertainties, risks, and advantages of these interventions and lead to more informed choices about cancer prevention strategies.

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ies of women at high risk for breast and ovarian malignancy. These data suggest that PCM may reduce breast cancer risk by 90%, PO may substantially reduce ovarian cancer risk, and 5 years of tamoxifen use may decrease contralateral breast cancer risk by 47%.

Previously, we developed a decision model to estimate the effect of prophylactic surgeries on survival of healthy BRCA1/2 mutation carriers, and, like other investigators, we found that young women could anticipate substantial life expectancy (LE) benefits from these procedures. However, many women in genetic testing programs already have had breast cancer. Therefore, we restructured our model to examine the survival benefit associated with PO, PCM, tamoxifen, and combinations of these strategies among women with breast cancer who are found to have BRCA mutations. To maximize clinical utility, we tailored survival estimates to individual prognostic parameters including age, BRCA mutation penetrance, and breast cancer prognosis.

### METHODS

**Model Design**

We developed a Markov state transition model to compare the survival benefits of secondary cancer prevention strategies for women with BRCA-associated breast cancer. The model simulates the natural history of hypothetical cohorts of women with newly diagnosed, unilateral BRCA-associated breast cancer who elect 1 of 8 strategies for prevention of second cancers: (1) careful surveillance; (2) 5 years of tamoxifen therapy; (3) PO; (4) PO and 5 years of tamoxifen therapy; (5) PCM; (6) PCM and 5 years of tamoxifen therapy; (7) both PO and PCM; and (8) PO, PCM, and 5 years of tamoxifen therapy. Simulations are repeated for women from prognostic groups defined by age at breast cancer diagnosis, the presence of cancer in axillary lymph nodes, and BRCA1/2 mutation penetrance. Each year, women in a cohort may succumb to their original primary breast cancer, develop contralateral breast cancer, develop ovarian cancer, or experience no adverse event. After a second primary breast or ovarian tumor develops, women are at risk of dying of these diseases. Data from the most recent life-tables for US women are used to incorporate the age-specific annual risk of dying from other causes. By tracking the proportion of patients developing cancers and/or dying each year, the computer simulation estimates LE and cause-specific mortality for cohorts of women who opt for each of the 8 cancer prevention strategies.

### 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 assumed that women with BRCA-associated breast cancer have the same prognosis, stage for stage, as women with sporadic breast cancer. The 1998 Oxford meta-analysis included more than 18,000 women and showed that premenopausal women who receive adjuvant therapy for axillary node–negative breast cancer have a 22% 10-year mortality, and that nodepositive women have a 47% 10-year mortality. However, many of the trials...
included were initiated in the 1970s, and stage-specific survival rates have been steadily increasing during the last 2 decades, an improvement largely attributable to screening and the resulting detection of small tumors. To account for these temporal trends and the improved breast cancer prognosis anticipated among women undergoing careful surveillance, we assumed that breast cancer mortality would be less than that observed in the Oxford meta-analysis and the US Surveillance and Epidemiology End Results (SEER) program. Instead, we assumed that women with BRCA-associated breast cancer would have mortality similar to participants in the Breast Cancer Detection Demonstration Project undergoing regular mammograms and breast examinations. Thus, in our model, primary breast cancer mortality for women with node-negative disease is 12% at 10 years and 17% at 20 years. For women with node-positive disease, breast cancer mortality is 26% at 10 years and 35% at 20 years. After 20 years, no additional primary breast cancer–related deaths occur.

Contralateral Breast Cancer. Several cohort studies suggest that women with BRCA-associated breast cancers have greater risk than women with sporadic breast cancers for developing contralateral tumors, which are likely to occur at young ages. However, the precise level of secondary cancer risk (whether contralateral breast or ovarian) depends on the underlying mutation penetrance. Estimates of BRCA1/2 penetrance have ranged from a cumulative primary breast cancer incidence of 36% to 85% in population-based series to 85% in women from the most dramatically affected families. Similarly, estimates of cumulative ovarian cancer risk have ranged from 12% to 63%.

Because mutation penetrance determines the underlying risk of developing contralateral breast cancer and ovarian cancer and therefore has great influence on the potential LE gain from prophylactic surgery, we performed separate simulations for cohorts of women carrying mutations with 3 prototypical levels of penetrance: low, moderate, and high. These 3 BRCA1/2 mutation penetrance levels are hypothetical and were chosen to represent the current range of estimates. We considered a high-penetrance mutation with 85% cumulative breast cancer incidence and 40% ovarian cancer incidence based on results reported by the Breast Cancer Linkage Consortium. We evaluated a moderate-penetrance mutation risk of 56% for cumulative breast cancer incidence and 16% for cumulative ovarian cancer incidence based on results from a study of BRCA1/2 mutations among Ashkenazi Jews in Washington, DC. Our prototypic low-penetrance mutation confers a 32% cumulative breast cancer risk based on small, population-based estimates and a 6% cumulative ovarian cancer risk based on the lower estimate of the 95% confidence interval from the Washington, DC, study.

Cumulative contralateral breast cancer incidence is estimated at 65% for women with high-penetrance BRCA1/2 mutations. We assumed that contralateral breast cancer incidence has the same proportional relationship to primary breast cancer incidence in women with low- and moderate-penetrance mutations as it does for women with high-penetrance mutations; thus, the cumulative contralateral breast cancer incidences we used in the base-case analysis were 43% for moderate-penetrance and 24% for low-penetrance mutations. BRCA-associated breast cancer patients are likely to undergo especially careful surveillance; therefore, we assumed an even more favorable stage distribution for contralateral breast cancers than that reported in the SEER program: 80% of cancers were detected while node-negative, and 20% were detected while node-positive but not yet metastatic to other sites. Stage for stage, we assumed that contralateral breast cancers have identical prognoses to primary breast tumors.

Ovarian Cancer. We assumed cumulative ovarian cancer incidences of 6%, 16%, and 40% for women with low-, moderate-, and high-penetrance mutations, respectively. Because of limited evidence that ovarian cancer screening favorably influences stage distribution, we considered, based on SEER data, that the probability of ovarian cancer being localized at the time of diagnosis is 25%; thus, in 75% of women, disease has spread beyond the ovaries at initial presentation. Lifetime ovarian cancer mortality is estimated at 17% for women diagnosed as having localized disease and 66% for women with advanced disease. All mortality due to ovarian cancer occurs within 15 years of diagnosis.

Effects of Cancer Prevention Strategies

Prophylactic Contralateral Mastectomy. Although no studies have measured the efficacy of prophylactic surgeries for known BRCA-mutation carriers, long-term follow-up from a recent large, case-control study of high-risk women suggests that PCM reduces breast cancer risk by 90%, and we used this estimate in our model. Women who originally had breast-conserving surgery and later elect PCM are likely to have simultaneous bilateral mastectomies to avoid asymmetrical cosmetic results. However, we considered that there was no survival benefit from mastectomy compared with lumpectomy and radiation for treatment of the affected breast. This means that all the survival benefit of bilateral mastectomies compared with usual, breast-conserving surgery and radiation is obtained from removing the healthy contralateral breast.

Prophylactic Oophorectomy. Since cases of papillary serous peritoneal tumors with histology identical to ovarian cancer have been reported following PO, it is evident that this procedure is an imperfect means of cancer prevention. However, there is some evidence to suggest that it reduces ovarian cancer risk and it is routinely discussed with women found to have BRCA1/2 mutations as a cancer prevention strategy. Based on expert consensus, we assumed a 50% reduction in ovarian cancer risk after bilateral PO and that the likelihood of detecting early-stage ovarian cancer on pathologic review of prophylactically removed ovaries was 1% of the age-specific ovarian cancer risk.
Although PO is an effective form of adjuvant breast cancer therapy, current oncology practice is to use either cytotoxic combination chemotherapy or hormonal agents. To reflect usual practice patterns, we assumed that for those women who had PO, this procedure would be performed in addition to, rather than instead of, usual adjuvant breast cancer therapy. It is possible that PO combined with standard chemotherapy may further decrease primary breast cancer mortality. However, because this has not yet been well established in randomized trials,37,38 we conservatively assumed that PO provides no additional protection from primary breast cancer recurrence and death.39

Recent evidence suggests that PO may decrease breast cancer incidence by as much as 50% among cancer-free women with BRCA1 mutations irrespective of hormone replacement therapy usage.40 Therefore, we considered the possibility that PO decreases the incidence of contralateral breast cancer in sensitivity analysis.

Without subsequent hormone replacement therapy, PO may have an adverse effect on mortality due to cardiovascular disease.41 Since young breast cancer survivors who choose to undergo PO may be candidates for hormone replacement therapy to minimize cardiovascular risk, we did not include excess cardiovascular mortality resulting from PO in our base case.42 However, in sensitivity analysis, we considered the possibility that PO increases cardiovascular mortality by as much as 35% among early-onset breast cancer survivors who do not take hormone replacement therapy.13-45

Tamoxifen. The 1998 Oxford meta-analysis compared effects of tamoxifen vs no tamoxifen in more than 37,000 women with primary breast cancer and with 15 years of follow-up showed that women who took tamoxifen for 5 years had a contralateral breast cancer risk reduction of 47% (95% confidence interval, 38%-56%).10 This benefit occurred in young, premenopausal women who received cytotoxic adjuvant therapy, as well as in older women. Moreover, it was also observed among the more than 8000 women who had primary tumors known to be estrogen receptor–poor. Although tamoxifen, as a means of preventing contralateral breast cancer, is most effective at preventing breast cancer recurrence in women whose tumors express estrogen receptors, it appears to be effective regardless of the receptor status of the original tumor.10

Based on results of the Oxford meta-analysis, we assumed that 5 years of tamoxifen therapy: (1) reduces the annual age-specific incidence of contralateral breast cancer by 47%; (2) increases annual mortality by 0.07% because of excess uterine cancers; (3) has no effect on mortality due to cardiovascular or thromboembolic disease, osteoporosis, or other disorders; and (4) provides no added reduction in primary breast cancer mortality for women treated with cytotoxic therapy.10 If longer-term follow-up data show that tamoxifen postpones rather than prevents contralateral breast cancers or is less effective in BRCA mutation carriers, our model overestimates this drug’s LE benefit.

Sensitivity Analyses
Sensitivity analyses were performed to assess the stability of results to variation in the base-case variable estimates. When several published point estimates were available for a particular parameter, we evaluated the full range of published estimates. Alternately, as in the case of the effectiveness of 5 years of tamoxifen therapy, we evaluated the upper and lower boundaries of the 95% confidence interval around our base-case estimate. In instances in which there were scant available published data and a large degree of uncertainty for a variable estimate (eg, the effectiveness of PO), we varied our base-case estimate over the broadest range that seemed plausible to the clinicians in our practice who counsel patients with BRCA1/2 mutations.

RESULTS
Impact of Tamoxifen and Prophylactic Surgeries on LE
Table 2 shows the total remaining LE for women with BRCA-associated breast cancer who were undergoing posttherapeutic surveillance and the gains in LE anticipated from different secondary cancer prevention strategies compared with surveillance. To provide results that are most clinically relevant, LE gains are presented according to age and axillary lymph node status at primary breast cancer diagnosis and for 3 levels of BRCA1/2 mutation penetrance.

The magnitude of potential LE gain from secondary cancer prevention strategies depends largely on the mutation penetrance—a measure of the risks of developing second cancers. For 30-year-old women diagnosed as having BRCA1/2-associated breast cancer not involving the axillary lymph nodes, total remaining LE ranges from 40.2 years for those with low-penetrance mutations to 34.5 years for those with high-penetrance mutations. Life expectancy gains from tamoxifen therapy range from 0.5 years (low-penetrance mutations) to 1.3 years (high-penetrance mutations). Life expectancy gains from PO range from 0.2 to 1.8 years, and from PCM they range from 0.9 to 2.1 years. Women who opt for both prophylactic surgeries could gain 1.1 to 4.2 years. The LE gains for women who elect combination strategies and who are diagnosed with primary breast cancer at different ages are shown in Table 2. Women who adopt 1 prevention strategy may experience relatively greater LE benefits from adopting an additional strategy, because they are more likely to be alive to realize those benefits. This explains why the gains for combination strategies may exceed the sum of the increases realized from each individual strategy (Table 2).

Gains in LE are consistently lower for women with node-positive disease than for women with node-negative disease. The worse the prognosis of the primary breast cancer, the lower the likelihood a woman will survive to reap the benefits of secondary cancer prevention. Similarly, the potential benefits from preventive strategies are more modest for older women because they have relatively fewer years of natural, remaining LE. Fifty-year-old women
with moderate-penetrance mutations can anticipate less than 1 year of survival benefit even if they have both surgeries. The LE gains for 60-year-old women are still more modest and for women who undergo both PO and PCM range from 2 weeks (low-penetration mutations) to 1.1 years (high-penetration mutations).

For a woman with newly diagnosed breast cancer, immediate rather than delayed prophylactic surgery yields the maximal gain in LE. However, some women learn that they carry a BRCA1/2 mutation years after their initial breast cancer diagnosis and may then wish to consider the survival benefits of prophylactic surgery. At any age, women previously diagnosed as having breast cancer who have remained free of recurrence experience somewhat greater gains in LE from prophylactic surgery than do women of the same age whose breast cancer is newly diagnosed. Both observations show that whether because of younger age or because they have demonstrated their ability to survive their initial breast cancer diagnosis, women with longer remaining LE will experience relatively greater benefits from secondary cancer prevention strategies.

To place our results in perspective, we compare these LE gains with those of women with sporadic breast cancer. For 30-year-old women with node-negative sporadic breast cancer, assuming a 9% lifetime probability of developing contralateral breast cancer and a 1.7% probability of developing ovarian cancer, the LE gain from tamoxifen to prevent contralateral breast cancer is less than 2 weeks; from PO to prevent ovarian cancer, less than 1 week; and from PCM, less than 1 month.

Our decision model can also be used to calculate how each cancer prevention strategy affects a woman’s chances of dying of breast or ovarian cancer vs other causes. Consider a cohort of 30-year-old node-negative breast cancer patients with moderate-penetrance BRCA1/2 mutations. Ultimately, 9% of women who chose surveillance, 5% who took tamoxifen, and 1% who chose PCM would die of contralateral breast cancer. Eight percent of women who opted for surveillance and 4% of those who underwent PO would eventually die of ovarian cancer. Irrespective of chosen cancer prevention strategy, more than 64% of women with moderate-penetrance BRCA1/2 mutations and node-negative breast cancer are expected to die of causes other than breast or ovarian malignancy.

**Sensitivity Analyses**

As shown in Table 2, LE gains are most influenced by variation in mutation type. LE gains for BRCA1/2-positive women with early-stage breast cancer are shown in Table 2. The table displays the change in life expectancy by strategy for women with node-negative and node-positive breast cancer for varying mutation types:

<table>
<thead>
<tr>
<th>Cancer Prevention Strategy</th>
<th>Life Expectancy, y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-Penetrance</td>
</tr>
<tr>
<td></td>
<td>Mutation</td>
</tr>
<tr>
<td>Node-Negative</td>
<td>Node-Positive</td>
</tr>
<tr>
<td>Prophylactic oophorectomy</td>
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</tr>
<tr>
<td>Contralateral mastectomy</td>
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</tr>
<tr>
<td>Both surgeries</td>
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<tr>
<td>Total life expectancy†</td>
<td>40.2</td>
</tr>
<tr>
<td>Surveillance‡</td>
<td></td>
</tr>
<tr>
<td>Total life expectancy‡</td>
<td>25.9</td>
</tr>
</tbody>
</table>

*Low-penetrance BRCA1 and BRCA2 mutations confer a cumulative contralateral breast cancer risk of 24% and a cumulative ovarian cancer risk of 6% by age 70 years. Moderate-penetrance mutations confer a cumulative contralateral breast cancer risk of 43% and a cumulative ovarian cancer risk of 16% by age 70 years. High-penetrance mutations confer a cumulative contralateral breast cancer risk of 65% and a cumulative ovarian cancer risk of 40% by age 70 years.

†Total life expectancy is remaining life expectancy presuming cancer surveillance without prophylactic surgery.

‡Change in life expectancy is the difference in remaining life expectancy between prophylactic surgical intervention and surveillance.
penetrance, age at diagnosis, and breast cancer prognosis. Sensitivity analyses were performed to assess the stability of model results to changes in other baseline probabilities and are shown in Table 3 for a cohort of 30-year-old women with moderate-penetrance BRCA mutations and node-negative breast cancer.

For model parameters other than age, mutation penetrance, and breast cancer prognosis, LE gains from secondary cancer prevention strategies are quite stable over broad ranges of plausible estimates (Table 3). Variation in contralateral breast cancer prognosis, contralateral breast cancer presenting at node-negative stage, ovarian cancer diagnosed at local stage, efficacy of PO and PCM, and efficacy of tamoxifen at preventing contralateral breast cancer each changed LE gains by less than 6 but more than 3 months. Variation in estimates of primary breast cancer prognosis and ovarian cancer prognosis changed LE gains by less than 3 months. Variation in estimates of tamoxifen’s effect on mortality due to uterine cancer, mortality due to thromboembolic and cardiovascular disease, mortality due to prophylactic surgical procedures, and of the frequency of incidental tumors diagnosed in prophylactic surgery specimens changed results by less than 2 weeks.

We did not incorporate either the potentially adverse effect of PO on cardiovascular mortality or a potential beneficial effect of this procedure on contralateral breast cancer incidence in our base-case analysis. Despite breast cancer history, young women who undergo PO may take subphysiologic hormone replacement therapy that provides adequate cardiovascular protection. However, if one assumes instead that women do not take hormone replacement therapy and that PO at age 30 years results in a 35% annual increase in cardiovascular mortality, this surgery provides only 0.4 (rather than 0.7) years of LE gain. If PO is assumed to decrease contralateral breast cancer incidence by 50%, it results in an estimated LE gain of 1.7 (rather than 0.7) years compared with surveillance. If PO both increases cardiovascular mortality by 35% and decreases contralateral breast cancer incidence by 50%, the net effect of this procedure is a 1.2-year LE gain compared with surveillance.

Finally, because follow-up data beyond 15 years are scarce, the durability of tamoxifen’s beneficial effect on contralateral breast cancer incidence is uncertain. If tamoxifen’s protective effect is assumed to last a lifetime, the LE gain is 0.9 years; if it lasts for 2 decades, the LE gain decreases to 0.6 years; if the duration of effect is only a decade, the gain is 0.3 years.

**COMMENT**

Women with breast cancer who present at a young age or have relatives affected by breast cancer may consider undergoing genetic testing for BRCA1/2 mutations. Those women who test positive for a mutation face difficult decisions about whether to undergo prophylactic surgery in an effort to decrease their risks of second cancers. Although few rush to undergo these drastic procedures, many nonetheless give careful consideration to their risks and benefits and consider available alternatives such as tamoxifen. Women with BRCA1/2 mutations who have already experienced a breast cancer diagnosis may view the trade-offs between quantity and quality of life differently than...
do cancer-free women and may have lower thresholds for choosing prophylactic surgery to avoid a second cancer diagnosis. Moreover, breast cancer patients may be motivated to seek BRCA testing specifically to make decisions about secondary cancer prevention.

Our decision analysis synthesizes what is currently known about the efficacy of prophylactic surgeries andtamoxifen chemotherapy as well as about cancer incidence and prognosis among BRCA1/2 carriers to provide tailored estimates of LE gain. It predicts that PCM and, to a lesser extent, PO and tamoxifen may substantially increase LE for young women with early-stage breast cancer and moderately or highly penetrant BRCA1/2 mutations. In contrast, young women with sporadic breast cancer gain less than 2 months’ LE from PCM and less than 1 week from PO, thus validating the standard medical practice of not recommending either PCM or PO for usual-risk breast cancer patients.

Because breast cancer patients with BRCA1/2 mutations have curtailed LEs as a result of their first malignancy, LE gains from prophylactic surgical interventions are lower for these women than are those estimated for similar-age, cancer-free women with BRCA1/2 mutations. However, for women with moderate- and high-penetrance mutations, they are comparable to the LE gains for adjuvant chemotherapy: 1.4 years for 45-year-old women with nodal-positive and 0.9 years for those with node-negative breast cancer. The LE gains from secondary cancer prevention strategies exceed those for many other, well-accepted preventive health measures, such as mammography, which provides normal-risk women with less than 0.7 years of LE gain. Therefore, balanced information that includes estimates of the magnitude of survival benefit from these interventions as well as their potentially adverse effects on quality of life should be discussed with patients, especially those who are young and have good prognoses.

For some women with newly diagnosed breast cancer, preoperative detection of a BRCA mutation may allow the opportunity to elect primary bilateral mastectomy with immediate reconstruction and consideration of PO as an alternative to standard breast cancer adjuvant chemotherapy. On the other hand, adding BRCA testing to the preoperative evaluation of women with positive family histories has the potential to exacerbate stress and, still worse, could precipitate hasty made decisions to undergo primary bilateral mastectomy.

Caution is warranted in interpreting our findings. First, the sensitivity of our results to penetrance makes it important that clinicians be updated on the most current information about mutation-specific cancer risks when considering how our estimates apply to individual patients. When mutation-specific risk is uncertain, the magnitude of survival benefit from prevention strategies should be considered across the spectrum of penetrance levels and in the context of an individual’s family history. Unfortunately, understanding of mutation-specific cancer risks is currently limited and precludes the possibility of providing women with more refined estimates of the LE benefits from secondary cancer prevention strategies. The sensitivity of our results to mutation penetrance underscores the need for further research to understand those factors that determine phenotypic expression of particular BRCA1/2 mutations. We considered 3 prototypical levels of penetrance; however, as additional information emerges about differences in the age-specific cancer risks associated with particular BRCA1 and BRCA2 mutations, our analysis will be updated.

Second, in the absence of good empirical data, we assumed that tamoxifen is just as effective at preventing contralateral breast cancer in women with BRCA mutations as it is in those without mutations. However, because tamoxifen appears to be most effective at preventing breast cancers that express estrogen receptors, and because BRCA-associated breast cancer appears more likely to lack estrogen receptors, it is conceivable that tamoxifen will be a less effective means of secondary cancer prevention for women with BRCA mutations than for women with sporadic breast cancers. Finally, we did not evaluate newer chemotherapeutic agents such as raloxifene because of the lack of long-term data on their effectiveness and toxicities, nor did we evaluate the use of oral contraceptives.

Clearly, survival is only 1 determinant of the net benefit of a cancer prevention strategy; effects on cancer-related anxiety, sexual and reproductive functioning, and self-image are also critically important. For some women, the negative impact of PM and PO on quality of life may outweigh even a potentially substantial increase in LE. For others, taking maximum steps to reduce the risk of a terrifying outcome such as ovarian cancer may result in a psychological benefit that outweighs even a very small survival benefit. Because our decision model is intended to facilitate decision making by individuals rather than to guide policy for populations, we have not quality adjusted LE gains. We present our results in terms of LE to help individual women weigh these effects and make highly personal assessments of how these interventions would affect their own lives.

For some patients and physicians, LE estimates derived from decision models may be a useful catalyst for discussion. Others will prefer a less quantitative approach. By synthesizing the best available relevant data, our model may help physicians convey the anticipated effects of various cancer prevention strategies on health outcomes for women with BRCA-associated breast cancer. Estimates derived from our model may be used as a springboard for patient-physician communication about a clinical situation for which there is no clear-cut algorithm and may encourage dialogue that helps breast cancer patients with BRCA1/2 mutations cope with uncertainty and make well-informed decisions about how to prevent second cancers.

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