Hereditary breast cancer: clinical features and risk reduction strategies

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Risk-reduction interventions for BRCA-related breast cancer are relevant not only for clinical decisions in breast cancer patients but also for healthy subjects who are potential candidates to undergo similar interventions. The literature on the impact of different surgical options and adjuvant systemic approaches aimed towards risk reduction for ipsilateral and contralateral breast cancer recurrences is briefly reviewed. Breast-conserving surgery is associated with a higher probability of local recurrence, but is counterbalanced by effectiveness of chemotherapy in reducing this risk. Consistent support for the hypothesis that antiestrogens are effective in reducing contralateral breast cancer risks is available from the literature. On the other hand, data on chemoprevention approaches for healthy subjects are too preliminary to draw any conclusions. Studies including conventional and newer hormonal drugs are needed to demonstrate the benefit of chemoprevention approaches. These may also deepen our knowledge on possible differences in the likelihood of clinical benefit to be expected among BRCA1- and BRCA2-altered tumours.

introduction

Approximately 0.1% of the population carries any of the 5000 different mutations reported for the BRCA genes, including both private and founder mutations [1, 2]. While originally estimated to be higher [3], a recent meta-analysis has reported rates of lifetime risk of breast cancer in the ranges 47%–66% and 40%–57% in BRCA1 and BRCA2 mutation carriers, respectively [4, 5].

Because of this increased breast cancer risk when compared with women not tested for these mutations, mutation carriers more frequently seek early detection strategies. They also often choose to undergo interventions aimed at cancer prevention or at reducing the incidence of additional cancers once an index cancer has occurred. These interventions range from frequent screening with mammogram, screening breast magnetic resonance imaging and clinical breast exams [6], to pharmacological therapy such as tamoxifen [7] or to risk-reduction surgeries such as prophylactic oophorectomy [8] and prophylactic mastectomy [8].

Evidence is emerging that the individual choices for risk-reducing interventions reflect the awareness of carrying a BRCA mutation. A recent survey study indicates that among women offered screening, the knowledge of carrying a positive BRCA mutation status was associated with the perception that prophylactic mastectomy was the most effective intervention to reduce risk, contrasting with the perception of women found not to carry a BRCA mutation (70% in BRCA+ women compared with 40% of BRCA– women, P < 0.001) [9].

risks of ipsilateral and contralateral breast cancer, after breast-conservation therapy in BRCA mutation carriers

After a breast cancer diagnosis in BRCA mutation carriers is established, the optimal local management remains an object of debate. BRCA-mutated carriers are likely to be more radiosensitive, as we and others originally suggested [10–12]; however, with adequate follow-up [11, 12], the lifetime risk of local recurrence in the index breast after breast-conservation therapy (BCT) tends to be greater in carriers than in women with sporadic breast cancer. This occurrence may be explained by a higher propensity for new cancers in carriers, since their mutation-related risks continue to affect the residual breast tissue (in both the ipsilateral and the contralateral breasts) after removal of the first index lesion.

A recent review by Liebens et al. [13] analyzed data in 20 studies to address the outcome after breast cancer diagnosis and treatment in mutation carriers. They critically reviewed the methodology, the characteristics of the populations, as well as the biases and confounding risk factors in the reported outcomes. All studies were retrospective, and patients undergoing mastectomy or lumpectomy plus radiation were included, with inevitable selection biases. With these limitations, the data indicate relatively consistent trends: in the majority of the studies assessed, hereditary breast cancer patients carried similar risks of ipsilateral recurrence (at least at
the time of reporting the data) and survival compared with patients with sporadic breast cancer (in 12/17 studies). An increased risk of contralateral breast cancer (CBC) in BRCA mutation carriers was present in 14 of 16 studies. Table 1 summarizes these results.

From a patient’s point of view, it is fundamental to establish whether mastectomy is a safer option for a mutation carrier. Several groups have addressed the role of BCT among BRCA mutation carriers and have compared outcomes after such surgery for hereditary and sporadic cancers. With BCT several concerns emerge: for instance, BRCA1/2 mutation is associated with an impairment of DNA repair and in vitro hypersensitivity to radiation of BRCA-null cells, as well as enhanced risks for potential radiation-induced complications, including second cancers [10, 11]. However, in three of the four studies, ipsilateral breast cancer recurrences were reported as being comparable to those in patients with sporadic breast cancers, perhaps because of the limited time of observation [14, 16, 17]. Table 2 summarizes the data from these initial studies: only the series reported by Haffty et al. [15] with the longest follow-up showed an increase in ipsilateral breast cancer recurrences after BCT among breast cancers arising in BRCA mutation carriers.

A more recent study from the European Institute of Oncology in Milan [18] indicated a significantly increased risk of local recurrence when hereditary breast cancer is treated with BCT. The study used a matched control design (same BCT treatment, age, tumor size and time of surgery) and reported the outcome of 54 patients with such hereditary breast cancers compared with 162 matched controls with sporadic breast cancer. Ten-year cumulative incidence of in-breast tumor recurrence (IBTR) was 27% for mutation carriers and 4% for sporadic breast cancer patients [hazard ratio (HR) 3.9; 95% confidence interval (CI) 1.1–13.8; \( P = 0.03 \)]. Ten-year cumulative incidence of CBC was 25% for mutation carriers and 1% for sporadic breast cancer carriers \( (P = 0.03) \). In their discussion, the authors identify possibly overestimating the risk of local recurrences in mutation carriers by conducting genetic testing at the time of recurrence. In their series, 8 of 11 carriers who had an IBTR \( (n = 6) \) or CBC \( (n = 5) \) were referred for genetic testing by their clinician only after presenting with these second events. Obviously, selecting subjects for testing at the time of recurrence increases the likelihood of a biased selection of high genetic penetrance cases among germline mutations.

While the studies described above compared local recurrence rates between hereditary and sporadic cancer patients, a recent study analyzed the outcome of different management strategies in a cohort of mutation carriers. Specifically, the rates of local control and survival after breast conservation versus mastectomy were analyzed in 655 mutation carriers [19] of whom 302 patients were treated with BCT and 353 with mastectomy. This study clearly demonstrated superior ipsilateral local control in mastectomy-treated women. It provided important insights about the pattern of local, regional and systemic recurrences in this population. Local failure as first failure was significantly more likely among those treated with BCT compared with mastectomy, with a cumulative estimated risk of 23.5% compared with 5.5%, respectively, at 15 years \( (P = 0.0001) \). The limitations of this study are inherent in its retrospective, non-controlled nature, susceptible to patients’ and physicians’ biased preferences between mastectomy and BCT. Because of finding different histologies from the original primary tumor and because of their non-adjacent geographical locations, most new events were likely second primary cancers rather than failure to control the original primary. As predicted, the risk of CBC was high in all groups, exceeding a 40% rate. There was no statistically significant difference in CBC when irradiated patients were compared with those who had not undergone radiotherapy (either post-mastectomy or as part of BCT), reassuringly indicating no added risk of secondary-radiation-induced tumors from scatter radiation, at a follow-up of 15 years.

The most important conclusion to be derived from this report is the fact that despite the higher local recurrence rate with BCT, the overall survival rates between the BCT and mastectomy groups did not differ significantly. Similarly, there was no difference in regional and systemic recurrences. These findings support the hypothesis that the inferior local control in the BCT group reflects the incidence of new tumors when significant residual breast tissue is left after BCT, instead of representing classical local recurrences, often heralding systemic spread. It also indicated that cautious surveillance of the conserved breast enabled early detection of new cancers, minimizing the impact on systemic outcome following the local treatment of these subsequent lesions.

### Table 1. Summary of results from studies comparing breast cancer outcome in sporadic and hereditary breast cancer [13]

<table>
<thead>
<tr>
<th>No. of studies with worse outcome for BRCA+</th>
<th>Local recurrence</th>
<th>Contralateral breast cancer</th>
<th>Disease-free survival, overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies with same outcome</td>
<td>5 14 5</td>
<td>12 2 12</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Risk of ipsilateral and contralateral recurrence after breast-conservation therapy in BRCA1/2 mutation carriers

<table>
<thead>
<tr>
<th>Patients ( (n) )</th>
<th>BRCA1/2 mutation carriers ( (n) )</th>
<th>Follow-up (years)</th>
<th>Local recurrence (%)</th>
<th>Contralateral breast cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robson et al., 1999 [14]</td>
<td>305</td>
<td>28</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Haffty et al., 2002 [15]</td>
<td>127</td>
<td>22</td>
<td>12.7</td>
<td>49</td>
</tr>
<tr>
<td>Robson et al., 2004 [16]</td>
<td>505</td>
<td>56</td>
<td>9.7</td>
<td>12</td>
</tr>
<tr>
<td>Pierce et al., 2006 [17]</td>
<td>605</td>
<td>160</td>
<td>7.9</td>
<td>12</td>
</tr>
</tbody>
</table>
In summary, BRCA1/2 mutation carriers with breast cancer have an elevated risk of a second in-breast event but such an occurrence does not significantly impact on the risk of systemic recurrence or shortened survival, relative to sporadic cases. CBC events were also very common [19]. The findings of this study warrant its inclusion in discussion with women on the different surgical treatment options, not only when BRCA mutation carriers are faced with decisions about the management of their first breast cancer but also in their decisions regarding undergoing risk-reducing strategies for both breasts.

**risks of ipsilateral and CBC recurrences after BCT in BRCA mutation carriers treated with systemic therapy**

The impact of different adjuvant cytotoxic therapies on clinical outcome in BRCA-mutated breast cancer patients has not been specifically addressed within clinical randomized studies. However, relevant information is contained in retrospective analyses within the literature review of Liemens et al. [13] on management of BRCA1/2-associated breast cancer. This review considered 15 clinical studies reporting data on risk of recurrence for BRCA-related breast cancer patients treated with adjuvant chemotherapy (CTX). Several methodological biases, such as lack of information on type of CTX, dose intensity, criteria for selection of CTX, concomitant hormone therapy, among others, pose problems in arriving at conclusions.

Metcalfe et al. [7] analyzed a series of 491 mutation carriers and showed a trend for an independent protective effect of chemotherapy on the risk of IBTR, in either BRCA1 or BRCA2 mutation carriers. Conversely, Pierce et al. [17] in a US case–control study and Robson et al. [16] in a cohort of Ashkenazi Jewish patients reported that CTX did not have any impact on IBTR. Liemens et al. [13] concluded their review by stressing that published evidence was inadequate to draw any conclusions on the effect of CTX on IBTR in such carriers.

More recently, the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer [19] retrospectively reviewed data on local failures as first events in BRCA mutation carriers recurrences while receiving or not receiving CTX after conservative primary surgery. BRCA mutation carriers treated with BCT had such events significantly reduced by CTX (from 23.5% to 11.9%), and this impact was also significant on multivariate analysis (odds ratio (OR) 5.5; 95% CI 2.3–13.3).

There is no support for an impact of CTX on risk reduction for CBC: the few studies [7, 16, 17] comparing clinical outcome of BRCA1-altered breast cancer patients with respect to the sporadic disease did not support the hypothesis for a specific benefit attributable to CTX. Recently, Pierce et al. [19] updated their previous analysis by the inclusion of a new large cohort of hereditary breast cancer patients and arrived at the same conclusions.

In summary, the hypothesis of a clinical benefit from CTX in reducing the risk of second in-breast failures for breast cancer in BRCA1 and BRCA2 mutation carriers seems plausible and also supported by recent evidence demonstrating that impaired DNA repair mechanisms related to BRCA alterations could increase the chemosensitivity of breast cancer [20, 21]. However, this effect cannot be confirmed on CBC and raises the question of why CTX would fail to have an effect in the latter circumstance. While this contradictory evidence may be a result of limited sample size and inherent methodological flaws, one could also hypothesize a role for biological diversity and aggressiveness in differently located sites of disease as contributing to a failure of CTX to impact on BCB recurrence.

Hormone therapy represents the most utilized adjuvant treatment of resectable breast cancer. The recent meta-analysis carried out by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) [22] strongly supports a benefit from hormonal therapy in reducing IBTR and CBC. However, in spite of trials involving >50,000 patients, data on effects of antiestrogens with respect to BRCA1/2 status are scanty. From Liemens et al.’s review [13] and by further updating the search on electronic databases, only four papers analyzing the clinical benefit of tamoxifen in women who carry a breast cancer with deleterious BRCA1/2 mutation were available.

Metcalfe et al. [7] analyzed a cohort of 491 breast cancer patients all carrying a deleterious BRCA alteration with a median follow-up of 9.2 years. In this series, tamoxifen (utilized in 30% of cases and for an unspecified number of years) demonstrated a trend for a protective effect (P < 0.08 at univariate analysis) on the risk of IBTR together with a risk reduction for CBC (HR 0.59, 95% CI 0.35–1.01) that did not differ in BRCA1 and BRCA2 mutation carriers.

Gronwald et al. [23] analyzed the impact of tamoxifen in a cohort of 1036 BRCA1/2-mutated breast cancer patients with or without contralateral occurrence of the disease. In this experience, the multivariate OR for CBC associated with tamoxifen use was 0.50 for BRCA1 mutation carriers (95% CI 0.30–0.85) and 0.42 for BRCA2 mutations carriers (95% CI 0.17–1.02) with a stronger protective effect lasting 5–10 years after primary surgery, particularly among premenopausal women.

Robson et al. [16] and Pierce et al. [17] using different methods of analysis compared the outcome of hereditary versus sporadic breast cancer patients treated with hormone therapy. Robson et al.’s cohort was confined to Ashkenazi Jewish patients: CBC risk was lower in BRCA1/2 mutation carriers receiving tamoxifen than in those not receiving the antioestrogen although this difference did not reach statistical significance. In the experience of Pierce et al., the effect of tamoxifen was found to be independent of mutation status but without any impact on risk of IBTR for the hereditary cohort (HR 0.29; P < 0.22). Conversely, the rates of CBC were significantly reduced by tamoxifen with an ~69% reduction of events among mutation carriers receiving the drug as opposed to those who did not (HR 0.31; P < 0.05).

Overall, we can speculate that adjuvant tamoxifen given to mutation carriers with breast cancer is effective in reducing the probability of contralateral recurrence. However, questions remain: is tamoxifen equally effective in BRCA1 and BRCA2 mutation carriers? Does tamoxifen prevent ER-positive tumors only? Are other hormonal agents effective in preventing locoregional recurrences?
Taken together, the choice of local and systemic therapies for primary breast cancer in BRCA-mutation-associated breast cancer may impact not only on systemic control but also on the specifically relevant local control. However, more data are needed to provide more precise guidance to patients.

**Chemoprevention for breast cancer risk reduction in healthy BRCA-altered subjects**

A comprehensive and updated review on the argument is available as part of the recently published ASCO Clinical Practice Guidelines on the Use of Pharmacologic Interventions for Breast Cancer Risk Reduction [24]. In fact, the scarce data on the efficacy of chemopreventive approaches to reduce BRCA alteration-related breast cancer risk can be extrapolated only from subset analyses of some large international randomized clinical trials utilizing chemoprevention strategies including tamoxifen, raloxifene and aromatase inhibitors to reduce breast cancer risk.

In NASBP-P1 trial [25], the effect of tamoxifen on breast cancer risk was addressed retrospectively in the hereditary subset. Unfortunately, in that trial, only 19 subjects known to have inherited BRCA1 or BRCA2 mutations received tamoxifen. Tamoxifen reduced (by 62%) breast cancer incidence among healthy BRCA2 mutation carriers similarly to the reduction in ER-positive breast cancer among all women entered in the trial. Conversely, a reduction in breast cancer incidence among healthy women with inherited BRCA1 receiving tamoxifen since age 35 was not seen. Overall, these results—albeit based on a small number of hereditary risk women (compared with nearly 6500 receiving tamoxifen versus placebo), raised two questions: (i) is tamoxifen able to reduce breast cancer risk among young BRCA mutation carriers? (ii) does the receptor profile of the breast cancers in these women reflect the impact of tamoxifen? This second consideration had already been discussed in relation to tamoxifen’s preventive action according to the receptor status of BRCA1- and BRCA2-associated cancers. In fact, these tumors differ in ER status and other biological features: BRCA1 mutation-related tumors lack hormone receptors and frequently exhibit a more aggressive behavior than do BRCA2 mutation-related tumors.

Tamoxifen could perhaps be viewed as being potentially effective in reducing cancer risk when BRCA2 is altered, but not when BRCA1 has mutations.

The only trial updated at ASCO [24] with some information on the BRCA status of their participants is the Royal Marsden Trial, which analyzed retrospectively the entire coding region of BRCA1 and BRCA2 genes in women who manifested breast cancer after tamoxifen preventive treatment. Unfortunately, also in their analysis an insufficient number of altered cases to determine the efficacy of tamoxifen by BRCA status was available.

Reviewing the evidence the ASCO Panel concluded that ‘the current limited evidence precludes reliable assessment of tamoxifen effects in this setting and, this issue is unlikely to be resolved by further analyses of already completed trials’. Furthermore the Panel reported that there are no data on the preventive effect of raloxifene and aromatase inhibitors specifically in BRCA mutation carriers. However, an interesting study, the Aromasin Prevention Study (Apre-S), randomizing postmenopausal unaffected BRCA1 and BRCA2 mutation carriers to the aromatase inhibitor exemestane or placebo is ongoing with an expected recruitment of >600 subjects.

**Surgical interventions on breast cancer risk: bilateral mastectomy and risk-reducing salpingo-oophorectomy**

In addition to the risk of ipsilateral breast cancer recurrence, breast cancer patients with a deleterious BRCA1 mutation can have up to a 43.4% 10-year risk of CBC while BRCA2 mutation carriers can have up to a 34.6% 10-year risk [6]. Tables 1 and 2 demonstrate the increased risk of CBC. The findings justify the practice of offering the option for risk-reducing surgery to women with BRCA mutations and intact breast (before any breast cancer diagnosis), since the risk of CBC is ~3% per year. Prophylactic bilateral mastectomy has resulted in up to 97% risk reduction of CBC [7, 26, 27]. Interestingly, the pattern of utilization of bilateral mastectomy differs widely between countries, reflecting providers’ biases in interpreting the evidence, communicating it and offering treatment options. It also reflects the diversity of the value systems affecting medical decision and health care delivery in differing countries [28].

An enhanced risk of ovarian cancer is well established in BRCA mutation carriers [29–31]. Risk-reducing salpingo-oophorectomy (RRSO) has demonstrated an impact on the risk of tubal–ovarian cancer [32–34] and has been reported to also reduce breast cancer [35].

Studies examining the extent of risk reduction by RRSO are often retrospective or case–control ones. Even the few prospective studies have different inclusion criteria and end points (risk of both breast and ovarian versus risk of either ovarian or breast cancer), as reflected by the wide range of results reported for risk reduction by RRSO, from 71% to 96%. A meta-analysis of 10 studies that reported the breast or gynecologic cancer outcomes in BRCA1/2 mutation carriers who had undergone RRSO has helped determine the evidence on this subject [37]. Breast cancer outcomes were investigated in three non-overlapping studies of BRCA1/2 mutations carriers, four of BRCA1 mutation carriers and three of BRCA2 mutation carriers. Gynecologic cancer outcomes were investigated in three non-overlapping studies of BRCA1/2 mutation carriers and one of BRCA1 mutation carriers. RRSO was found to be associated with a statistically significant reduction in risk of breast cancer in each subset of BRCA mutation carriers. Table 3 summarizes these results. Specifically, in BRCA1/2 mutation carriers the HR was 0.49; 95% CI 0.37–0.65. Similar risk reductions were observed in BRCA1 mutation carriers (HR 0.47; 95% CI 0.35–0.64) and in BRCA2 mutation carriers (HR 0.47; 95% CI 0.26–0.84). RRSO was also associated with a statistically significant reduction in the risk of BRCA1/2-associated ovarian or Fallopian tube cancer (HR 0.21; 95% CI 0.12–0.39). Data were insufficient to obtain separate estimates for ovarian or Fallopian tube cancer risk reduction with RRSO in BRCA1 or BRCA2 mutation carriers.
Table 3. Results of risk-reduction salpingo-oophorectomy in BRCA mutation carriers [30]

<table>
<thead>
<tr>
<th>BRCA mutation</th>
<th>Breast cancer risk reduction</th>
<th>Tubal–ovarian cancer risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/2</td>
<td>0.49</td>
<td>0.21</td>
</tr>
<tr>
<td>BRCA1</td>
<td>0.47</td>
<td>0.21</td>
</tr>
<tr>
<td>BRCA2</td>
<td>0.47</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Data were insufficient to obtain separate estimates for ovarian or Fallopian tube cancer risk reduction with risk-reduction salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. CI, confidence interval; HR, hazard ratio.

In summary, both prophylactic bilateral mastectomy and RRSO result in reduction of breast cancer in mutation carriers. A comprehensive discussion with the patient regarding the many options available is central to the management of mutation carriers, and requires a sustained commitment by the provider to update their experience, while waiting for the literature to generate new insights into the clinical implications of these mutations.

**utilization and comparative effectiveness of risk reduction strategies**

Metcalfe et al. [28] described the different patterns of utilization of the various risk prevention strategies in differing countries: 2677 women with BRCA mutations in nine countries were contacted and asked to complete a questionnaire about the treatment they had chosen. The questionnaire was completed a mean of 3.9 years since the results of genetic testing (range 1.5–10.3 years). Fifty-seven percent (1531 women) had bilateral prophylactic oophorectomy. Only 18% of the mutation carriers who had never had breast cancer had prophylactic bilateral mastectomy (248/1383); mutation carriers in the USA and Holland most frequently chose prophylactic bilateral mastectomy, 36.3% and 32.7%, respectively, compared with rates of 2.7% and 4.2% in Poland and Israel. Pharmacological prevention with tamoxifen was chosen by 5.5% while raloxifene was the preventive measure in 0.47%. Noticeably, this survey also showed that approximately half of the mutation carriers had not undertaken any risk reduction intervention, relying solely on screening and early detection.

In 2000, Schrag et al. [38] examined the effect of tamoxifen therapy, RRSO and prophylactic contralateral mastectomy (PCM), and combinations of these strategies on the life expectancy of women after developing unilateral breast cancer in the presence of a BRCA1 or BRCA2 gene mutation. The study was meant to provide quantifiable information to carriers making decisions about risk reduction. From published series the probabilities of developing CBC and ovarian cancer, dying from these cancers, dying from primary breast cancer, and the reduction in cancer incidence and mortality due to prophylactic surgery and/or tamoxifen were estimated. They then modeled seven strategies, including 5 years of tamoxifen use, RRSO and PCM and a combination of these strategies, compared with careful surveillance. Compared with surveillance alone, a 30-year-old early-stage breast cancer patient with BRCA mutations would derive a gain in life expectancy of 0.4–1.3 years from tamoxifen therapy, 0.2–1.8 years from RRSO and 0.6–2.1 years from PCM. Older age and poorer prognosis from primary breast cancer attenuated these gains [38].

More recently, informed by a more updated review of the literature, Anderson et al. [39] found that for BRCA1 or BRCA2 mutation carriers, prophylactic surgery or chemoprevention leads to better survival than surveillance alone. This study evaluated the cost-effectiveness of the preventive strategies that are available to unaffected women carrying a single BRCA1 or BRCA2 mutation with high cancer penetrance by applying Markov modeling with Monte Carlo simulations and probabilistic sensitivity analyses. 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) were sources of survival data.

The value of different interventions, including tamoxifen, oral contraceptives, bilateral salpingo-oophorectomy, mastectomy, both surgeries or surveillance was assessed.

The study found that for mutation carriers 35 years of age who underwent both surgeries (prophylactic bilateral mastectomy and oophorectomy) there was 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. Older age at intervention increased the cost-effectiveness of prophylactic mastectomy for BRCA1 mutation carriers to $73 755 per life-year. 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.

In conclusion, the management of BRCA mutation carriers is evolving: it reflects the available evidence as well as the bias of different ethical value systems and structural characteristics of the different health care systems operating worldwide. It is also a model for genetic cancer medicine heralding the impact of genetics on other medical circumstances likely to emerge as knowledge on the causes of cancer is impacted by the wide use of genomics.

**disclosures**

The authors have declared no conflict of interest.

**references**
