Review

Breast cancer in BRCA mutation carriers: breast-conserving therapy or bilateral mastectomy?

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Practice Points

- Often, the first decision made by BRCA mutation carriers with newly diagnosed breast cancer is whether to have breast-conserving therapy (BCT) or bilateral mastectomy.

- Testing for a BRCA mutation should be considered in breast cancer patients with a relevant personal or family history of cancer, those aged <50 years and patients with triple-negative cancers aged <60 years.

- A relevant family history includes the occurrence of breast cancer at an early age in multiple relatives in more than one generation, as well as the occurrence of bilateral breast cancer, male breast cancer or associated cancers; for example, ovarian cancer or Jewish ancestry.

- Increased rates of ipsilateral breast tumor recurrence (IBTR) and contralateral breast cancer (CBC) are seen following BCT in BRCA mutation carriers; however, more extensive surgery has not been proven to improve survival.

- Advances in operative techniques and breast reconstruction, with associated reductions in morbidity and hospital stay, mean that bilateral mastectomy is now a more acceptable treatment for BRCA mutation carriers with breast cancer.

- Adjuvant chemotherapy and risk-reducing salpingo-oophorectomy can modify the risk of IBTR and CBC in BRCA mutation patients who choose to undergo BCT. Breast surveillance with mammography and MRI is recommended following BCT.

- Geographical location often determines the treatment strategy adopted by BRCA mutation carriers diagnosed with breast cancer. Patients in the USA are more likely to undergo risk-reducing salpingo-oophorectomy and bilateral mastectomy.
BRCA1 patients aged <50 years will benefit most from bilateral mastectomy. BCT is an adequate treatment for BRCA2 patients aged >50 years. The increased risk of IBTR and CBC should be discussed with patients treated with BCT.

SUMMARY: BRCA mutation carriers who are diagnosed with breast cancer can be overwhelmed with decisions. The choice between breast-conserving therapy, mastectomy or a bilateral mastectomy is often the first to be made by patients. Those who choose breast-conserving therapy are faced with an increased risk of ipsilateral breast tumor recurrence and contralateral breast cancer; however, choosing more extensive surgery increases surgical morbidity without a proven survival advantage. Additional factors that influence surgical decision-making are the use of adjuvant therapy, the role of risk-reducing salpingo-oophorectomy and the biology of the breast cancer. Advances in surgical techniques, breast reconstruction and screening must also be considered when choosing the surgical treatment for breast cancer patients with a BRCA mutation.

Hereditary breast cancer accounts for 5–10% of breast cancer cases, and a BRCA mutation has been found in 2.0–4.7% of patients with breast cancer [1–2]. It is estimated that <1% of the general population carry a mutation of BRCA1/2 (BRCA1: 0.04–0.24%; BRCA2: 0.14–0.4%) [1–3]. Crude calculations suggest that 500,000–1 million people in the USA carry a mutation of BRCA1/2. The carriage of a BRCA mutation is associated with a significantly increased risk of developing cancer. Estimates place the cumulative risk of breast cancer to the age of 70 years at 46–65% for BRCA1 mutation carriers and 43–45% for BRCA2 mutation carriers [4–5]. The risk of ovarian cancer is approximately 39% in BRCA1 mutation carriers and 11% in BRCA2 mutation carriers [5].

Strategies aim to manage the increased risk of breast and ovarian cancer in healthy BRCA mutation carriers. Early detection of a BRCA mutation enables implementation of appropriate screening or therapeutic measures. Breast cancer screening with annual MRI and mammography beginning between 25–30 years of age, or 10 years before the age of the earliest first-degree relative with breast cancer, is currently recommended by the National Comprehensive Cancer Network and the American College of Radiology [101,102]. However, screening does not prevent breast cancer; it aims to detect it at an early stage in order to maximize the chance of successful treatment and reduce mortality [6–7]. On the other hand, risk reduction aims to reduce the occurrence of breast or ovarian cancer. Large chemoprevention studies, in mainly postmenopausal women, have shown that tamoxifen and raloxifene can reduce the incidence of breast cancer [8–10]. However, the acceptance of hormonal chemoprevention in premenopausal women is low, owing to its side-effect profile [11]. Prophylactic risk-reducing surgery is increasingly employed: bilateral risk-reducing salpingo-oophorectomy (RRSO) is advisable for all BRCA mutation carriers upon completion of childbearing. It almost eliminates the risk of ovarian cancer and can reduce the incidence of breast cancer by half [12–13]. Prophylactic bilateral risk-reducing mastectomy (RRM) may reduce the occurrence of breast cancer to <2% [14] and <1% [15–17] in women with a BRCA mutation after 4.5–8.5 years of follow-up. Complication rates after RRM are not insignificant; in one series, 49.6% of RRM patients had a complication following reconstruction [15].

BRCA mutation carriers diagnosed with breast cancer face numerous additional treatment choices. Data demonstrate similar long-term survival between patients with early breast cancer treated with breast-conserving therapy (BCT) or a mastectomy [18,19]. However, the increased risk of ipsilateral breast tumor recurrence (IBTR) and contralateral breast cancer (CBC) lead many BRCA mutation patients to choose mastectomy with a contralateral prophylactic mastectomy (CPM). The preventative role of RRSO, and the use of adjuvant radiotherapy, chemotherapy and hormonal therapy, involve additional considerations in BRCA mutation carriers. Screening
following BCT is also different. In this review, we summarize evidence that may guide the decisions that BRCA mutation carriers and their physicians face following a diagnosis of breast cancer. We consider how these choices are influenced by their location, cultural values and family history of cancer.

**Identifying a BRCA mutation in patients with breast cancer**

It is important to identify breast cancer patients who are BRCA mutation carriers because this can greatly influence treatment choices. A BRCA mutation may be suspected owing to family history, tumor biology or demographics.

Personal or family history traits suggesting hereditary breast cancer include the occurrence of breast cancer at an early age in multiple relatives in more than one generation, as well as the occurrence of bilateral breast cancer, male breast cancer or associated cancers; for example, ovarian cancer or Jewish ancestry [102]. The recently revised UK National Institute for Health and Care Excellence guidelines recommend the use of an accepted calculation method when considering family history and carrier probability [103].

The pathologic features of estrogen receptor-negative (ER), triple-negative, high-grade breast cancers are frequently found in BRCA1 mutation carriers [20]. Genetic testing of women with triple-negative breast cancer (TNBC), <50 years of age, without a family history of breast cancer, has identified a BRCA mutation in 19 (11/58) and 23% (11/47) of patients in two recent series [21,22]. Universal genetic testing of all women diagnosed with breast cancer could be considered if cost was not a factor [23]. The American Society of Breast Surgeons’ position statement recommends BRCA testing in women with “early-onset breast cancer” (diagnosed before the age of 50 years) and <60 years of age with TNBC [104]. The updated UK National Institute for Health and Care Excellence guidelines do not specifically recommend genetic testing based on a patient’s age at diagnosis of breast cancer or in patients with TNBC; however, they recommend that “clinicians should seek further advice from a specialist genetics service for families containing (a patient with) TNBC under the age of 40 years” [103].

BRCA testing has recently evolved; although standard sequencing of BRCA1/2 was found to detect 95.3% of mutations in high-risk Ashkenazi Jewish patients (owing to the high prevalence of three founder mutations), comprehensive testing for large gene rearrangements is required to detect 21.4% of BRCA mutations in high-risk Latin–American/Caribbean patients [24].

**Is BCT adequate in BRCA mutation carriers?**

The feasibility of BCT in BRCA mutation carriers can be judged by comparing the rates of recurrence and survival with those of patients without BRCA mutations. These rates can also be compared between BRCA mutation patients treated with BCT or a unilateral or bilateral mastectomy. The stage at diagnosis of breast cancer is important; in advanced cancers, outcomes will be mainly influenced by the index cancer. Any benefit obtained from prophylactic surgery will be reduced.

Numerous studies examining IBTR, CBC and survival in BRCA mutation patients have been performed, and these have been comprehensively reviewed [25–27]. However, studies often have limitations in their methodology, which make them less relevant for today’s BRCA mutation patient.

Most studies are retrospective, from a single institution, contain a small number of patients, and are biased in their patient selection and design. Survivorship bias is common when BRCA testing is performed on patients who have been treated in the past; if only survivors are included in the study, the outcomes of the patients who died will not be examined and survival rates will be artificially high. Ascertainment bias can occur if genetic testing is preferentially performed on breast cancer patients who develop IBTR or CBC; testing at this point is more likely to detect a BRCA mutation, and the rates of IBTR or CBC will be artificially inflated.

Most evidence suggests that the rate of IBTR following BCT is higher in BRCA mutation patients compared with patients who do not have a BRCA mutation. IBTR is also higher in BRCA mutation carriers who are treated with BCT compared with those who have a mastectomy (Table 1). There is also an increased risk of CBC in BRCA mutation patients compared with those who are not BRCA mutation carriers (Table 1).

- **IBTR, CBC & survival in BRCA mutation carriers with breast cancer**

In 2002, Haffty and colleagues reported high rates of IBTR and CBC following BCT in BRCA mutation carriers [28]. They retrospectively studied
290 women aged ≤42 years who underwent BCT between 1975 and 1998. Genetic testing was performed in 127 of 234 survivors who were alive in 2000 and revealed a BRCA mutation in 22 patients. The rate of IBTR at 12 years was 49% in BRCA mutation carriers and 21% in patients with sporadic cancer (p = 0.007). The rate of CBC at 12 years was 42% in BRCA mutation carriers versus 9% (p = 0.001) in patients with sporadic breast cancer. However, patients in this study did not receive optimum treatment by today’s standards; surgical margins were unknown in 50% of BRCA mutation carriers, 18% had no axillary surgery, and none received adjuvant hormonal therapy. Survivorship bias in patient selection is present.

In 2007, Brekelmans and colleagues found that the 10-year actuarial risk of IBTR after BCT was similar in BRCA1 and BRCA2 mutation carriers (16 and 17%, respectively) compared with non-BRCA hereditary breast cancer and sporadic breast cancer patients (15 and 21%, respectively) [29]. The median follow-up in all groups was between 4.3 and 5.1 years, and analyses were performed to correct for survivorship bias. The 10-year actuarial risk of CBC was higher in BRCA mutation carriers (25% for BRCA1 and 20% for BRCA2 mutation carriers) compared with non-BRCA hereditary breast cancer and sporadic breast cancer patients (6 and 5%, respectively; p ≤ 0.001 compared with BRCA2 associated cancers). There were no differences

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Groups</th>
<th>Surgery type</th>
<th>n</th>
<th>Follow-up (years)</th>
<th>IBTR</th>
<th>CBC</th>
<th>BCSS (%)</th>
<th>Overall survival (%)</th>
<th>Ref.</th>
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<td>Haffty et al. (2002)</td>
<td>BRCA1/2</td>
<td>BCT</td>
<td>22</td>
<td>12</td>
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<td>42.0</td>
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<td>21.0</td>
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<td>Brekelmans et al. (2007)</td>
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<td>BCT or Mast</td>
<td>223</td>
<td>10</td>
<td>16.0</td>
<td>25.0</td>
<td>NS</td>
<td>62.0</td>
<td>50.0</td>
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<td>BRCA2</td>
<td>BCT or Mast</td>
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<td>0.001</td>
<td>Compared with BRCA2</td>
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<td>≤0.001</td>
<td>Compared with BRCA2</td>
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<td>4.0</td>
<td>1.0</td>
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<td>Pierce et al. (2010)</td>
<td>BRCA1/2: BCT versus Mast</td>
<td>BCT</td>
<td>302</td>
<td>10</td>
<td>10.5</td>
<td>3.5</td>
<td>0.0001</td>
<td>Overall 23 after 8 years</td>
<td>93.6</td>
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<td></td>
<td></td>
<td>Mast</td>
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<td>3.5</td>
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<td>93.5</td>
<td>91.8</td>
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<td>5.5</td>
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<td>91.7</td>
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<td></td>
<td>Mast</td>
<td>353</td>
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<td></td>
<td>92.8</td>
<td>89.8</td>
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<td>BCT</td>
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<td>12.9</td>
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<td>81.1 at mean 10.5 years</td>
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<td>15.8</td>
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<td>BCT or Mast</td>
<td>810</td>
<td>10</td>
<td>NR</td>
<td>22.0</td>
<td>78.8 at mean 11.1 years</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td></td>
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<td>BCT or Mast</td>
<td>15</td>
<td>33.8</td>
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No p-values for differences in BCSS and overall survival were statistically significant.
BCSS: Breast cancer-specific survival; BCT: Breast-conserving therapy; CBC: Contralateral breast cancer; IBTR: Ipsilateral breast tumor recurrence; Mast: Mastectomy; NA: Not applicable; NR: Not recorded; NS: Not significant.
in the rates of overall or disease-specific survival between the studied groups. On multivariate analysis, the administration of adjuvant chemotherapy and performing RRSO, but not CPM (or bilateral mastectomy), were prognostic factors for breast cancer-specific survival.

In 2009, Garcia-Etienne et al. reported an estimated cumulative risk of IBTR following BCT of 27% in BRCA mutation carriers at 10 years, compared with 4% for sporadic controls (p = 0.03) [30]. The estimated risk of CBC was 25% for mutation carriers at 10 years compared with 1% for sporadic controls (p = 0.03). However, the median follow-up in this retrospective study was 4 years; only three BRCA mutation carriers and four control patients were followed up for 10 years. The total number of IBTRs in BRCA mutation patients was small at only six. Ascertainment bias was evident — most (73%) BRCA mutation carriers had genetic testing performed after IBTR or CBC occurred.

In 2010, after reviewing 25 retrospective trials, Bordeleau et al. concluded that most studies showed similar rates of IBTR at 5 years following BCT in BRCA mutation carriers and patients with sporadic breast cancer; however, divergence was seen after 5 years [26]. The 10-year rate of CBC was increased in BRCA mutation patients compared with those with sporadic cancer, estimated to be 20–42% versus 5–6%, respectively. The authors noted that recent studies with less methodological limitations have not demonstrated a significant overall survival difference between BRCA-associated and sporadic breast cancers.

Liebens and colleagues reviewed 20 trials in which breast cancer, treated with BCT or mastectomy, were compared [27]. The risk of IBTR was increased in BRCA mutation carriers compared with sporadic breast cancer patients in five out of 17 studies, despite varying designs and biases. An increased risk of CBC was seen in BRCA mutation patients in 14 out of 16 studies. Most studies (11/14) did not show reduced overall survival (or breast cancer-specific survival) for BRCA mutation carriers compared with sporadic controls.

In 2010, Lee et al. performed a systematic review and meta-analysis of the effect of a BRCA mutation on breast cancer survival [31]. Retrospective trials with varying designs, containing data from patients diagnosed from the 1980s–2000s, were included. On the basis of six studies (383 patients) and four studies (312 patients), respectively, they concluded that both short- and long-term survival were decreased in BRCA1 mutation carriers compared with sporadic controls. Based on five studies (234 patients) and two studies (142 patients), respectively, they did not find a difference in short- or long-term survival in BRCA2 patients compared with those with sporadic breast cancer.

In 2012 Goodwin et al. compared the prognosis of 94 patients with a BRCA1 mutation and 72 with a BRCA2 mutation to a cohort of 1550 patients with sporadic breast cancer [32]. On multivariate analysis, after a mean follow-up of 7.9 years, the rates of distant disease recurrence and death were not different in BRCA mutation carriers compared with sporadic controls, after adjusting for the more aggressive tumor features in the BRCA2 group.

IBTR, CBC & survival in large multi-institutional studies

Larger multi-institutional studies have revisited the rates of IBTR and CBC in BRCA mutation carriers. In 2010 Pierce and colleagues reported treating 655 BRCA mutation patients from nine institutions with either BCT (n = 302) or mastectomy (n = 353) [33]. IBTR occurred in 11.6% (35/302) of patients treated with BCT and 3.1% (11/353) treated with mastectomy after 8.2 and 8.9 years of follow-up, respectively (p = 0.0001). Estimated IBTR rates were greater at all time points in patients treated with BCT compared with a mastectomy: 4.1 versus 1.4% at 5 years, 10.5 versus 3.5% at 10 years and 23.5 versus 5.5% at 15 years. When BCT patients received adjuvant chemotherapy (n = 219; 72.5%), their estimated 15-year rate of IBTR fell from 43.7 to 10.7% (p < 0.0001), not statistically different from the 5.5% rate in mastectomy patients (p = 0.08). The nature of IBTR was available for 23/35 BCT patients; most (16/23) IBTRs were considered to be second primary cancers because they occurred in a different breast quadrant and/or had a different histology. Excluding 12 women with synchronous breast cancer, 23.0% (148/643) of BCT and mastectomy patients developed CBC. CBC rates were similar in patients treated with or without adjuvant radiotherapy (p = 0.44), suggesting that radiation scatter did not result in increased CBC in BCT patients. The patients treated with BCT were more often premenopausal (79.5 vs 55.8%; p = 0.003). BRCA1 mutation carriers...
(65.2 vs 55.8%; p = 0.01) and less likely to be ER-positive (29.8 vs 35.7%; p = 0.006); however, more had stage I breast cancer (52.3 vs 41.1%; p = 0.0007). The authors recognized potential survivorship and ascertainment biases in this study. It is not surprising that a survival disadvantage in BCT patients was not found. In the Early Breast Cancer Trialists’ Collaborative Group overview, a reduction in 15-year breast cancer mortality was only demonstrated when there was a substantial (>10%) difference in local recurrence at 5 years [34].

In 2011 Metcalfe et al. studied the risk of IBTR following BCT in 396 BRCA mutation carriers. These were ≤65 years of age and had stage I or II breast cancer diagnosed between 1975 and 2008 at ten cancer genetic clinics [35]. The actuarial risk of ipsilateral breast cancer was 5.8% after 5 years, 12.9% after 10 years and 15.8% after 15 years of follow-up. On multivariate analysis, three factors significantly reduced the rate of IBTR; adjuvant chemotherapy (received by 70.2%; relative risk [RR]: 0.45; 95% CI: 0.24–0.84; p = 0.01), RRSO (performed on 33.3%; RR: 0.33; 95% CI: 0.13–0.81; p = 0.02) and radiotherapy (received by 87.4%; RR: 0.28; 95% CI: 0.12–0.63; p = 0.002). The average interval between the initial breast cancer and IBTR was 7.5 years, suggesting that the majority of these were second primary cancers rather than recurrence of the original cancer. To reduce survivorship bias, the authors included BRCA mutation patients who had died and women who were not tested from families with a documented BRCA mutation (n = 33; 8.3%).

In 2011, Metcalfe and colleagues also reported the risk of CBC in 810 BRCA mutation patients treated with BCT or mastectomy. These were from the same genetic clinics, and similar methods were used in this trial [36]. CBC occurred in 149 patients (18.4%) after a mean follow-up of 11.1 years. The actuarial risk of CBC was 13.1% after 5 years, 22.0% after 10 years and 33.8% after 15 years of follow-up. Women <50 years of age were significantly more likely to develop CBC than those >50 years of age after 15 years (37.6 vs 16.8%; p = 0.003). Bilateral RRSO in 60.4% (489/810) of patients reduced the RR of CBC to 0.48 (95% CI: 0.27–0.82; p = 0.002). The decrease in CBC following RRSO was only observed in patients <50 years of age. On multivariate analysis, prior radiation therapy (BCT) did not increase the risk of CBC, nor did prior chemotherapy or hormonal therapy reduce the risk of CBC.

Other factors influencing surgical treatment choices in BRCA mutation carriers

Additional influences on the surgical treatment of breast cancer in BRCA mutation patients with breast cancer are summarized in Table 2.

- Adjutant & neoadjuvant treatment in BRCA-associated breast cancer

The role of adjuvant treatments can affect surgical choices in BRCA mutation carriers with breast cancer. In vitro studies have found that hypersensitivity to radiation may be displayed by BRCA-deficient cells. Concerns have been expressed that irradiated breast tissue remaining after BCT may be at an increased risk of radiation-induced complications, including recurrent or second cancers; for example, angiosarcomas [37]. This is difficult to establish clinically; although studies have found increased IBTR after BCT [33,35], they do not show increased CBC (owing to radiation scatter) in BRCA mutation carriers [33,36]. BRCA mutation patients treated with BCT may undergo a mastectomy at a later stage, if they develop an IBTR or if they elect to have one for risk reduction. Following prior radiotherapy, mastectomy and immediate reconstruction with tissue expander/implant-based techniques had a 70% complication rate and a 60% success rate in a recent series [38]. Radiotherapy should be avoided if a bilateral mastectomy is being considered; the administration of adjuvant chemotherapy following breast-conserving surgery is a convenient solution [104]. At completion of chemotherapy, patients may subsequently commit to BCT by receiving radiotherapy or choose to undergo mastectomy instead.

Adjutant chemotherapy and endocrine therapy do not influence local surgical treatment for BRCA mutation carriers to the same extent as radiation therapy. However, when BRCA mutation carriers treated with BCT received adjuvant chemotherapy, their risk of IBTR was reduced as described previously [33,35]. Adjutant chemotherapy did not influence the occurrence of CBC in two large series [33,36]. Endocrine therapy did not reduce the rates of CBC or IBTR.

Arun et al. recently reported their experience treating BRCA mutation patients with
Breast cancer in *BRCA* mutation carriers: breast-conserving therapy or bilateral mastectomy?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Potential influence on surgical treatment</th>
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<tr>
<td><strong>Adjuvant therapy</strong></td>
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</table>
| RT     | BRCA cells: *in vitro* hypersensitivity to RT, increased potential for second cancers [37]  
RT did not increase the rate of CBC in cohort studies [33,36]  
Increased complication and failure rates if future mastectomy and reconstruction [38,45]  
Initial BCS and chemotherapy an option in patients undecided on BCT or mastectomy [102] |
| CT     | Reduced IBTR following BCT [33,35]  
No reduction in rate of CBC [33,36] |
| Hormonal therapy | No reduction in rate of IBTR or CBC [33,35,36] |
| Neoadjuvant CT | High rate of pCR in *BRCA1*, triple-negative and trastuzumab-treated patients [39] |
| RRSO   | Reduced occurrence of ovarian cancer but not further breast cancer [40]  
Risk of IBTR following BCT reduced by two-thirds [35]  
Risk of CBC reduced by half following BCT or mastectomy [36] |
| Surgical outcome |  |
| NSM    | Enhanced acceptability of unilateral/bilateral mastectomy in selected patients [43]  
Largest reported series raises concerns about oncologic safety [44] |
| Direct-to-implant reconstruction | Low complication and reoperation rates achieved in one-stage reconstruction [45] |
| Inpatient stay | Reduced inpatient stay with multidisciplinary postoperative care [50] |
| **Tumor biology & age** |  |
| *BRCA1* versus *BRCA2* | TNBC more likely in *BRCA1* [20] |
| Age and CBC | Increased risk of CBC in patients diagnosed <50 years of age compared with >50 years of age [51] |
| **Breast screening** |  |
| MRI    | Increased sensitivity compared with mammography alone. Smaller cancers detected in *BRCA2* mutation carriers [7]  
Increased tumor growth rate in *BRCA2* mutation carriers and patients <40 years of age [52]  
Despite limited information on role of MRI following BCT, this strategy is recommended [8,102] |
| **Decision-making** |  |
| Geographical variation | *BRCA* mutation patients in the USA are more likely to undergo RRSO and prophylactic contralateral mastectomy [55,57]  
High uptake of RRSO and prophylactic mastectomy in *BRCA* mutation carriers in the USA and Denmark [57,58] |
| Online decision tool | Complex statistical models available for *BRCA* mutation carriers, not yet for *BRCA* mutation patients with breast cancer [60,61] |


neoadjuvant chemotherapy [39]. From 1997 to 2009, 317 patients treated with neoadjuvant chemotherapy for breast cancer underwent *BRCA* testing. The rates of pathologic complete response (pCR) were 46% (26/57) for *BRCA1* mutation carriers, 13% (3/23) for *BRCA2* mutation carriers and 22% (53/237) for patients without a *BRCA* mutation. Multivariate analysis found that a higher rate of pCR was achieved in *BRCA1* mutation carriers, ER-negative cancers and patients treated with trastuzumab. No difference in survival was found between groups at a median follow-up of 3.2 years. Although useful for increasing BCT rates, 89.5% (51/57) of *BRCA1* mutation patients and 95.6% (22/23) of *BRCA2* mutation carriers who received neoadjuvant chemotherapy had a mastectomy.

- **Prophylactic RRSO**

On meta-analysis, Rebbeck et al. confirmed that RRSO reduced the risk of breast cancer (hazard ratio [HR]: 0.49; 95% CI: 0.37–0.65) and tubal-ovarian cancer (HR: 0.21; 95% CI: 0.12–0.39) in *BRCA* mutation carriers [12]. All prospective studies included in this meta-analysis, except one, included *BRCA* mutation carriers with prior breast cancer in their ovarian cancer analysis. In 2010, Domchek and colleagues reported their prospective cohort study investigating the effects of prophylactic surgery on cancer risk.
and mortality in 2482 BRCA mutation carriers [40]. These were identified between 1974 and 2008 in 21 genetic centers in Europe and North America. Of these, 10% (257) underwent RRM and 40% (993) underwent RRSO. Those who underwent RRSO had reduced all-cause (HR: 0.40; 95% CI: 0.26–0.61), breast cancer-specific (HR: 0.44; 95% CI: 0.26–0.76) and ovarian cancer-specific mortality (HR: 0.25; 95% CI: 0.08–0.75). However, in patients with prior breast cancer (mean age: 44.8 years), the risk of further breast cancer was not reduced by RRSO. Further breast cancer occurred in 11.1% (23/208) of patients who had RRSO and 13.7% (60/439) of patients who did not (HR: 1.00; 95% CI: 0.56–1.77). In the multi-institutional studies described above, the rates of IBTR and CBC were reduced in patients who underwent RRSO [35,36].

Reconstruction considerations following unilateral or bilateral mastectomy

Semple et al. studied the international rates of breast reconstruction following mastectomy in BRCA mutation carriers; most (69.5%) BRCA mutation carriers had breast reconstruction performed [41]. Not surprisingly, this was more likely in younger women and those without breast cancer. BRCA mutation carriers undergoing unilateral or bilateral mastectomy have often been faced with significant morbidity and reoperation rates related to breast reconstruction [5]. The complication rate in patients with unilateral breast cancer has been demonstrated to be approximately double in patients who have a bilateral mastectomy performed compared with a unilateral mastectomy [42]. However, recent developments in operative and reconstructive techniques may improve outcomes and acceptability of bilateral mastectomy in BRCA mutation carriers with breast cancer.

Nipple-sparing mastectomy (NSM) has become increasingly popular. A recent series from our institution reported the results of 353 NSMs in 200 patients [43]. Of these, 157 (44%) were therapeutic procedures: for invasive cancer in 82 cases (23.2%); ductal carcinoma in situ in 74 cases (20.8%); and a phyllodes tumor in one case. A BRCA mutation was present in 11.6% (14/121) of patients undergoing therapeutic NSM and 27.8% (22/79) undergoing prophylactic NSM. In this series, complication rates were low; infection occurred in 2% (six breasts), skin desquamation developed in 19.5% (which required debridement in 3.3%) and implant loss occurred in 1% (three patients). Our main objective when performing NSM is to remove all breast tissue; further follow-up is necessary to establish oncological safety in our series. The long-term safety of NSM has not yet been established in breast cancer patients, and especially not in BRCA mutation carriers. The largest series of NSMs to date reported local recurrence in 5.1% (48/934) of patients after a median follow-up of 4.2 years [44]. The number of BRCA mutation carriers in this series was not reported. Most (83%) patients were treated for invasive cancer and 77% (37/48) of local recurrences in invasive cancer occurred in the breast, but not in the nipple–areola complex (which received intraoperative radiotherapy). This highlights that an adequate incision must be made when performing NSM to allow removal of the same amount of breast tissue that would be removed in a conventional mastectomy.

Immediate direct-to-implant reconstruction may further improve the acceptability of bilateral mastectomy for patients who wish to avoid multiple surgical procedures. In a recently published series, 460 direct-to-implant reconstructions were performed with acellular dermal matrix in 260 patients [45]. The number of BRCA mutation carriers in this series was not reported. These were oncological procedures in 148 (32%) cases and prophylactic in 318 (68%) mastectomies. Early complications occurred in only 3.9% (18 breasts); implant loss in 1.3% (six breasts), skin necrosis in 1.1% (five breasts), hematoma in 1.1% (five breasts), infection in 0.4% (two breasts) and capsular contracture in 0.6% (three breasts). A further 15.2% of patients without a complication underwent elective revisional surgery, in most cases to exchange the implant for a larger size. It was noted that the complication rate in this series was fourfold higher in irradiated breasts.

The psychosocial aspects of performing BCS or mastectomy should be considered. BCS with radiotherapy may provide a more acceptable treatment for the majority of patients with early breast cancer. However, although numerous studies have examined quality-of-life outcomes after breast cancer surgery, results are inconsistent [46], and these may be less relevant to BRCA mutation patients. In one study of 1957 women, patients who were treated with a mastectomy, or mastectomy with reconstruction, reported
Breast cancer in BRCA mutation carriers: breast-conserving therapy or bilateral mastectomy?

Review

The age of a BRCA mutation carrier or patient with breast cancer is an important consideration when the extent of therapeutic or prophylactic treatments is being discussed. Verhoog et al. studied the effects of developing CBC in 164 breast cancer patients from 83 families with a proven BRCA1 mutation [51]. The 10-year actuarial risk of CBC was 40% in 124 patients diagnosed aged <50 years of age versus 12% in 40 patients diagnosed >50 years of age (p = 0.02). These data suggest that the role of CPM is especially important in young (<50 years of age) BRCA1 mutation carriers diagnosed with breast cancer. This is confirmed by the findings of Metcalfe and colleagues that found that women <50 years were significantly more likely to develop CBC than those >50 years of age at 15 years (37.6 vs 16.8%; p = 0.003) [36]. Additionally, decreased RR of CBC following RRSO was only observed in patients <50 years of age.

Breast cancer screening following BCT or unilateral mastectomy

BRCA mutation carriers with breast cancer who undergo BCT are recommended, by the American Society of Breast Surgeons, to have breast screening that includes MRI [104]. Data from three large MRI breast cancer screening studies have recently been combined, to include 1275 BRCA mutation carriers [5]. Important differences in the natural history of breast cancer in patients with BRCA1 and BRCA2 mutations were found; cancers in BRCA2 mutation carriers were smaller (80% were ductal carcinoma in situ or invasive cancers ≤10 mm, compared with 49% for BRCA2 mutation carriers; p < 0.001). Additionally, below the age of 40, only one in 25 cancers diagnosed in BRCA1 mutation carriers was diagnosed by mammography alone, compared with seven of 11 cancers diagnosed in BRCA2 mutation carriers (p < 0.0001). These findings may be partly explained by earlier findings from the same three trials; tumor volume doubling times were found to be greatest in patients with BRCA1 mutations, and in women aged ≥40 years [52]. One of these three trials included [6] and two excluded [53,54] patients with a prior history of breast cancer; in total, only 7.1% (90/1275) had prior breast cancer. The Canadian MRI study, which included 18.2% (90/496) of patients with prior breast cancer, found that the sensitivity of MRI was 86% over the entire study compared with 19% for mammography [6]. Of the 57

Biological features & age of breast cancer in BRCA mutation carriers

The Consortium of Investigators of Modifiers of BRCA1/2 has uncovered important differences in the pathology of breast cancer, in BRCA1 (4325 patients) and BRCA2 (2568 patients) mutation carriers [20]. The median age of breast cancer diagnosis was 40 years for BRCA1 mutation carriers and 43 years for BRCA2 mutation carriers. TNBCs were found in 69% of BRCA1 patients compared with 16% of BRCA2 mutation patients. In the future, treatment decisions for BRCA mutation carriers may not just be concerned with choosing different breast and ovarian surgeries, but may be more focused on tumor biology, and the pathological differences between BRCA1 and BRCA2 mutation carriers.

a worse body self-image, more physical symptoms and discomfort around the surgical site, and a greater negative impact on their sexuality compared with those who underwent BCS [47]. Qualitative research has demonstrated that patients evaluate their reconstruction on how normal they feel, how normal they believe they appear, how they felt cared for by their practitioners, whether reconstruction helped complete their ‘cancer journey’ and whether complications occurred [48]. In BRCA mutation patients, the benefits of performing bilateral mastectomy are greater compared with a patient with sporadic breast cancer. With evolving breast reconstruction options, and newer, holistic methods of evaluating patients’ quality of life following breast surgery [49], the psychosocial effects of BCS versus bilateral mastectomy in BRCA mutation patients with breast cancer need to be re-evaluated.

In parallel to the decreasing complication rates, the length of stay in hospital following mastectomy has reduced with improvements in postoperative multidisciplinary care. In a recent series from Memorial Sloan-Kettering Cancer Center (NY, USA), 82.7% (444/537) of patients were discharged from hospital on the first day following unilateral mastectomy [50]. This report did not examine how many patients carried a BRCA mutation. Bilateral mastectomy patients are now routinely discharged on the first day following surgery at Memorial Sloan-Kettering Cancer Center. This may also help improve the acceptability of mastectomy in BRCA mutation carriers with breast cancer.

Breast cancer in BRCA mutation carriers: breast-conserving therapy or bilateral mastectomy?

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cancers detected, 53 were screen detected, one was an interval cancer and three were incidental findings at prophylactic mastectomy. The cancers detected were early stage; 79% were ductal carcinoma in situ or invasive cancers ≤1 cm and 91% were node negative. Despite the growing body of evidence for MRI screening for healthy BRCA mutation carriers, its role in BRCA mutation patients who have undergone BCT or unilateral mastectomy is less clear. Guidelines suggesting MRI follow-up after BCT in BRCA mutation patients appear prudent.

**Decision-making in BRCA mutation carriers and risk prediction tools**

BRCA mutation carriers and their physicians are faced with difficult decisions upon the diagnosis of breast cancer. The extent of surgery to the breast(s), benefits of prophylactic RRSO and advantages and disadvantages of adjuvant therapies must be considered. The treatment decisions made by BRCA mutation patients vary depending on their location, age and whether the diagnosis of a BRCA mutation was made before or after the cancer diagnosis. Metcalfe et al. compared the uptake of CPM in 927 patients diagnosed with breast cancer prior to realizing that they were BRCA mutation carriers. Overall, 27.3% (253/927) had a CPM with a mean follow-up of 4.1 years [55]. Only 7.9% of CPMs were performed at the time of the initial breast cancer and 92.1% were performed during a second surgery. The rate of CPM was 49.8% (153/302 patients) in the USA, 28.0% (89/318) in Canada and only 4.9% in Europe and Israel (15/307). North American patients who underwent CPM were more likely to be younger, to have had an initial mastectomy to treat the breast cancer and to have had a prophylactic RRSO. Schwartz and colleagues found that when genetic testing was performed preoperatively, following a diagnosis of breast cancer, 48% (15/31) of women diagnosed with a BRCA mutation chose to undergo bilateral mastectomy [56]. Interestingly, 24% (33/136) who tested negative for a BRCA mutation also underwent bilateral mastectomy.

Metcalfe and colleagues in 2008 also studied the international variation in uptake in preventative options in BRCA mutation carriers [57]. Their cohort contained 2677 women; 1294 (48.3%) with a prior unilateral breast cancer and 1383 (51.7%) without, who were followed up for a median 3.9 years after genetic testing. The overall bilateral RRSO rate was 57.2% (1531/2677). RRSO was performed on 71.1% of women (500/703) in the USA, 57.3% (439/766) in Canada and 45.3% (592/1308) in Europe/Israel. The rate of bilateral prophylactic mastectomy for those without cancer was 36.3% in the USA, 22.4% in Canada and 6.7% in Europe/Israel. However, approximately half of the European patients studied were from a single institution in Poland. In healthy Danish BRCA mutation carriers, the estimated 10-year uptake of bilateral RRSO was 75%, and the estimated uptake of prophylactic bilateral mastectomy was 50% [58]. In the USA, RRM and RRSO have been found to be more common in healthy BRCA mutation carriers who had a deceased first- or second-degree relative from breast cancer [59].

Complex statistical modeling has been used to develop an online tool to aid decision-making in healthy BRCA mutation carriers [60]. This simulates the probability of a BRCA mutation carrier developing cancer, overall survival and disease-specific mortality from the age of 25–70. The model examines the effects of no intervention, screening with mammography and MRI, prophylactic oophorectomy or mastectomy and the age at which these are performed. The outcomes estimated are the incidence of breast and ovarian cancer, the likely tumor features, what treatment is necessary and overall survival. This model has been used to estimate the gains in life expectancy attained from undergoing screening and prophylactic surgeries [61]. When prophylactic mastectomy and oophorectomy are performed immediately after the diagnosis, the gain in life expectancy is estimated to be 6.8–10.3 years for BRCA1 mutation carriers and 3.4–4.4 years for BRCA2 mutation carriers. Performing screening alone with mammography and MRI is estimated to increase life expectancy in BRCA1 mutation carriers by 1–9.9 years and in BRCA2 mutation carriers by 1.5–4.3 years. A similar model is not yet available for BRCA mutation carriers who have been diagnosed with breast cancer to help guide their treatment choices. Such a model would involve even more complex statistical considerations, and entail estimates and assumptions that are not yet fully understood. Limitations of this prediction model for healthy BRCA mutation carriers have been recognized [62]. The model makes assumptions on the penetrance of BRCA.
mutations and the incidence of cancers at each age range, which may be overestimated or, perhaps worse, underestimated for individuals with a stronger family history. Another concern is that the beneficial effects of screening and treatments may be overestimated; for example, although MRI screening may detect breast cancer at a relatively small size, the prognosis of an aggressive basal type cancer in a \textit{BRCA1} mutation carrier may not be as good as the model predicts.

\textbf{Conclusion & future perspective}

Patients with hereditary breast cancer make up a small proportion of the total population diagnosed with breast cancer. \textit{BRCA} mutation carriers, who are included in this group, have been extensively investigated in numerous publications. The limitations and biases of earlier reports with small numbers of participants have been overcome through multi-institutional cooperation and collaboration.

A \textit{BRCA4} mutation should be considered when a patient is newly diagnosed with breast cancer. At present, we selectively test patients based on their personal and family history of cancer, and ethnicity (described earlier). There are differences in USA and UK guidelines on the genetic testing of young women with breast cancer and patients with TNBC. It is possible that, in the future, universal genetic testing will be performed for all women with breast cancer; however, the cost of this is prohibitive at present.

When a \textit{BRCA} mutation is identified, the type of breast cancer surgery must be carefully considered and discussed. Recent, large, multicentric studies have confirmed that BCT is associated with a higher risk of IBTR, but a survival advantage has not been demonstrated following more radical surgery. Strategies to reduce the risk of IBTR in \textit{BRCA} mutation carriers who insist on BCT include the administration of adjuvant chemotherapy, RRSO and not foregoing radiotherapy. The rate of CBC is higher in \textit{BRCA} mutation carriers, and this is the rationale for performing CPM. RRSO can also reduce the rate of CBC in \textit{BRCA}-associated breast cancer.

The effects of adjuvant treatments, the risk of surgical morbidity, and the effectiveness of future breast screening are also important in deciding the type of breast cancer surgery in \textit{BRCA} mutation carriers. Adjuvant radiotherapy in BCT can reduce the success and increase the complication rate if a future mastectomy and reconstruction are performed. In \textit{BRCA1} patients who are motivated to pursue BCT, neoadjuvant chemotherapy can result in a high rate of pCR. Surgical guidelines now suggest that \textit{BRCA} mutation carriers who have BCT should be followed up with screening MRI and mammography. For patients who want to pursue bilateral mastectomy and reconstruction, it is now more acceptable, and its complication rate and length of hospital stay have decreased. There are deficits in our knowledge that need to be addressed by further research. Despite a lack of long-term data demonstrating the oncologic safety of NSM, it has exploded in popularity. The role of NSM needs to be clarified in general breast cancer patients and in \textit{BRCA} mutation carriers. The role of MRI screening in \textit{BRCA} mutation carriers who have undergone BCT also needs further evaluation.

The decisions made by \textit{BRCA} mutation patients and their doctors vary depending on their geographic location and cultural values. \textit{BRCA} mutation patients with breast cancer in the USA are more likely to have a bilateral mastectomy and undergo bilateral salpingooophorectomy. The same is true for prophylactic surgery in healthy \textit{BRCA} mutation carriers; however, the rate in Danish carriers has now equaled that in the USA. An online decision-making tool is available to help \textit{BRCA} mutation carriers make decisions. The development and validation of a decision-making tool for \textit{BRCA} mutation patients diagnosed with breast cancer seems an obvious future extension of this project; however, the complexity needed to produce this may be prohibitive.

There is no robust evidence to suggest that the prognosis of \textit{BRCA} mutation patients with breast cancer is worse than patients with sporadic breast cancer. In addition, \textit{BRCA} mutation carriers who undergo BCT do not have worse overall survival. \textit{BRCA1} patients <50 years of age are more likely to have aggressive TNBC, their tumor growth rate is faster and MRI screening is less beneficial compared with \textit{BRCA2} mutation carriers; these will benefit most from bilateral mastectomy. Motivated \textit{BRCA} mutation patients who are most suitable to be treated with BCT are those who are older (>50 years of age), do not have a strong family history of breast cancer, will receive adjuvant chemotherapy, undergo RRSO and participate in MRI screening. They should be willing to accept an increased risk of IBTR and CBC, which may require further treatment.
in the future. BCT is an adequate treatment in BRCA2 patients >50 years of age.

Finally, one of the most important developments in the last decade is the increased cooperation and collaboration between investigators of BRCA1 mutation carriers. Through these efforts, future prospective, multi-institutional studies may continue to provide high-quality evidence to improve outcomes for BRCA1 mutation carriers with breast cancer.

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest


- Combined analysis of three studies that show the benefits of using MRI screening in BRCA1 mutation carriers.


- The Consortium of Investigators of Modifiers of BRCA1/2 identified important differences between the pathologic features of cancers in BRCA1 and BRCA2 mutation carriers.


Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.
Large multi-institutional study that investigated the risk of ipsilateral breast tumor recurrence and contralateral breast cancer following breast-conserving therapy (BCT) or mastectomy in BRCA mutation carriers with breast cancer.


A large multi-institutional study that examined the factors associated with ipsilateral breast tumor recurrence in BRCA mutation patients treated with BCT.


A large multi-institutional study that examined the factors associated with contralateral breast cancer in BRCA mutation patients treated with BCT or mastectomy.


A prospective multi-institutional cohort study that investigated the role of risk-reducing surgery in BRCA mutation carriers.


Large multi-institutional study that investigated the risk of ipsilateral breast cancer: clinical features and risk reduction in BRCA1/2 families as compared with sporadic breast cancer cases.


Use of a novel prediction model to estimate cancer risk in BRCA1 mutation carriers and the effects of screening and risk-reducing interventions.


### Websites

101. American College of Radiology

