Local approaches to hereditary breast cancer

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The diagnostic and local treatment modalities of hereditary breast cancer (HBC) are evolving based on emerging evidence from new imaging, radiotherapy and surgical studies. The optimal selection of diagnostic and therapeutic strategies for the individual HBC patient remains an area of active research in this relatively new patient population. In this context, some rational pathways of intervention are currently available to both reduce cancer risk in mutation carriers without a cancer diagnosis, as well as to reduce the risk of recurrence or new cancers among the carriers already diagnosed with a malignancy. It is encouraging to notice to what degree certain interventions have successfully reduced both the risk of malignancy and the anxiety associated with this genetic diagnosis. This updated report aims at summarizing the most recent findings, while it identifies the areas of uncertainty that remain, and continue to present difficult challenges, particularly among younger HBC patients.

Key words: hereditary breast cancer, radiation, BRCA1, BRCA2, radiation-induced malignancy

introduction

In 2012, it is estimated that there will be 226,870 new cases of invasive breast cancer diagnosed among women in the United States [1]. This projected incidence includes carriers of mutations in the BRCA, p53, PTEN/MMAC, CHEK2 and ATM genes that have been associated with breast cancer. BRCA mutation carriers constitute the majority of these, with ~1 in 1000 American women carrying at least 1 of the 5000 reported BRCA mutations [2, 3]. The lifetime risk of developing breast cancer for these women ranges from 47%–66% and 40%–57% in BRCA1 and BRCA2 mutation carriers, respectively [4, 5]. While all mutation carriers share similar needs and concerns regarding breast and other cancers, it is helpful to divide these patients into two groups: (i) healthy women found to carry a BRCA mutation in the absence of detectable cancer and (ii) breast cancer patients who are either known BRCA carriers or who are identified as having a BRCA mutation after the diagnosis of breast cancer.

Healthy BRCA mutation carriers, generally alerted by their family history, tend to self-select to choose early genetic assessment. They often represent a unique group of young women, highly motivated to offset the risk associated with their genetic diagnosis. Understandably, they are interested in reliable early detection strategies. To enhance early detection, frequent clinical breast exams, screening mammography, and magnetic resonance imaging (MRI) are routinely offered to these women [6]. At this point, no early detection tools available completely prevent the risk of mortality due to breast cancer in BRCA populations. It is understandable that more and more often, these women chose prophylactic strategies, including surgery to reduce their risk of developing malignancies. Pharmacologic endocrine therapy, e.g. tamoxifen has been shown to reduce breast cancer incidence in large cohorts of mainly postmenopausal women [7, 8]; however, in premenopausal women, its uptake is limited by its side-effect profile [9] and its role remains unproven. Prophylactic oophorectomy conveys the double benefit of reducing incidence of both breast and ovarian cancer [10] and has proven to be widely acceptable [9]. Bilateral prophylactic mastectomy can almost eliminate the occurrence of breast cancer in BRCA carriers, reducing the rate to <2% in some series [11, 12]. The popularity of this option varies widely based on geography, reflecting cultural and social biases among both patients and health care providers.

A breast cancer diagnosis in a known or newly diagnosed BRCA carrier poses additional treatment options and dilemmas. Increased rates of ipsilateral breast tumor recurrence (IBTR) and contralateral breast cancer (CBC) have been found in studies comparing outcomes in BRCA-associated versus sporadic breast cancers [13]. While breast-conserving therapy (BCT) will be desired by some patients, mastectomy can reduce the occurrence of IBTR [14] and prophylactic contralateral mastectomy can address the risk of CBC. Therefore, these treatment options should be discussed with patients.

Appropriate counseling does change treatment decisions; following preoperative confirmation of a BRCA mutation, 48% (15 of 31) of patients chose to undergo bilateral mastectomy in one series [15]. The recommendations for adjuvant radiotherapy, chemotherapy and endocrine treatment involve different considerations in BRCA patients. Bilateral oophorectomy, which has been abandoned in sporadic breast cancer, also remains an important adjunct in mutation carriers.

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strategies for early detection in BRCA mutation carriers

It is recommended that women with BRCA mutations undergo self-breast exam training and perform monthly breast exams starting at age 18, with semiannual clinical breast exams starting at age 25 [16]. However, a study of 236 Canadian women with proven BRCA mutation demonstrated that clinical breast exams alone are not particularly sensitive, with only 9.1% of the cancers detected being appreciated on examination [6]. The addition of mammography significantly improved the ability to detect cancer, with an increase in detection sensitivity to 45%, and a specificity of 99.8%. Over the years, concerns about the potential harm of ionizing radiation, as well as the decreased sensitivity of mammography in younger women with dense breasts, have generated interest in both ultrasound and MRI as alternative imaging modalities. The sensitivity of ultrasound alone for detecting breast cancer in BRCA mutation carriers has been reported to be 33%–40% in clinical screening series [6, 17]. While most series report a high specificity associated with ultrasound (>90%), MRI can diagnose breast cancers that would be missed by ultrasound and/or mammography alone. Warner et al. reported that the addition of MRI to a regimen of mammography, ultrasound and regular clinical breast exams increased the sensitivity from 65% to 95% in 236 Canadian mutation carriers [6]. Long-term results of this comprehensive screening trial were recently reported [18]. With a total of 1837 screening rounds over a 12-year period in 496 women, 57 cancers were detected with 97% of these being stage 0 or 1. Only 1 of 28 previously unaffected women diagnosed with invasive cancer died from breast cancer following relapse of a 3-cm, node-positive cancer diagnosed on her first screen (annual breast cancer mortality rate of 0.5%). Three patients died of other causes and none of the 24 surviving patients had a distal relapse after a median of 8.4 years since cancer diagnosis. This and other evidence have led the National Comprehensive Cancer Network (NCCN) to develop its recommendation for mammographic and MRI screening beginning at age 25 for BRCA mutation carriers [19].

Many are concerned about this NCCN recommendation because exposure to radiation is not without inherent risks. In the general population, ionizing radiation is a known risk factor for developing breast cancer and this risk increases with earlier age of exposure [20]. BRCA1 and BRCA2 encode for proteins that are instrumental in error free, homologous recombination (HR)-mediated repair of DNA double-strand breaks [21–23]. Concerns that ionizing radiation may have deleterious effects in women with defects in DNA repair, including BRCA mutation carriers have been raised [24, 25]. It has been hypothesized that BRCA mutations carriers are especially vulnerable to the DNA damage produced by ionizing radiation. To address this, Pijpe et al. conducted a large retrospective cohort study (GEN-RAD-RISK) of 1993 BRCA mutation carriers from France, the UK and the Netherlands, accrued between 2006 and 2009 [26]. The risk of breast cancer was estimated using a time-dependent, estimated cumulative breast radiation dose, based on the reported frequency of diagnostic procedures. Any exposure to ionizing radiation before age 30 years was associated with a higher risk of breast cancer, hazard ratio 1.9 [95% confidence interval (CI) 1.2–3.0]. Increases in breast cancer risk were observed with increases in the estimated cumulative radiation dose: <0.0020 Gy, ≥0.0020–0.0065 Gy, ≥0.0066–0.0173 Gy and ≥0.0174 Gy corresponded to hazard ratios of 1.63 (95% CI 0.96–2.77), 1.78 (95% CI 0.88–3.58), 1.75 (95% CI 0.72–4.25) and 3.84 (95% CI 1.67–8.79), respectively. A single-view diagnostic mammogram delivers a dose of 0.004 Gy; therefore, the cumulative radiation dose in BRCA carriers aged <30 years may approach levels that can increase the risk of breast cancer. The findings from this study warrant caution in prescribing any imaging associated with ionizing radiation exposure in this population.

risk-reducing salpingo-oophorectomy

BRCA mutation carriers are faced with an increased risk of ovarian cancer in addition to breast cancer [4, 27, 28]. Risk-reducing salpingo-oophorectomy (RRSO) not only effectively reduces the risk of tubal-ovarian cancer [29–31], but it also decreases the risk of breast cancer [32]. In a seminal study, women who underwent RRSO had significantly reduced all-cause mortality (3% versus 10%; HR 0.40, 95% CI 0.26–0.61), breast cancer–specific mortality (2% versus 6%; HR 0.44, 95% CI 0.26–0.76) and ovarian cancer–specific mortality (0.4% versus 3%; HR 0.21, 95% CI 0.06–0.80), compared with women who did not [33]. Most studies examining the extent of risk reduction conferred by RRSO have been case–control or retrospective in nature. Unfortunately, the few prospective studies reported in the literature have different inclusion criteria and end points (risk of both breast and ovarian cancer or cancer of either alone), leading to a wide range in reported risk reduction, from 71% to 96%. In order to better determine the available evidence, Rebeck et al. [34] executed a meta-analysis of 10 studies that reported the cancer outcomes in BRCA1/2 mutation carriers who had undergone RRSO. Breast cancer outcomes were investigated in four nonoverlapping studies of BRCA1 mutation carriers, three studies of BRCA2 carriers and three studies of unspecified BRCA1/2 mutations. Gynecologic cancer outcomes were investigated in three nonoverlapping studies of BRCA1/2 mutations and one study of BRCA1 mutation carriers. There was a statistically significant reduction in the risk of breast cancer following RRSO across all mutation subtypes as summarized in Table 1. In BRCA1/2 mutation carriers

Table 1. Results of risk-reduction salpingo-oophorectomy in BRCA mutation carriers [34]

<table>
<thead>
<tr>
<th>BRCA</th>
<th>Breast cancer risk reduction HR</th>
<th>95% CI</th>
<th>Tubal-ovarian cancer risk-reduction HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/2</td>
<td>0.49</td>
<td>0.37–0.65</td>
<td>0.21</td>
<td>0.12–0.39</td>
</tr>
<tr>
<td>BRCA1</td>
<td>0.47</td>
<td>0.35–0.64</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>BRCA2</td>
<td>0.47</td>
<td>0.26–0.84</td>
<td>N/A</td>
<td>N/A</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.
carriers, the HR was 0.49 (95% CI 0.37–0.65), with similar risk reductions observed in BRCA1 carriers (HR 0.47, 95% CI 0.35–0.64) and in BRCA2 carriers (HR 0.47, 95% CI 0.26–0.84). There was also a statistically significant reduction in the risk of tubal-ovarian cancer in BRCA1/2 carriers who underwent RRSO (HR 0.21, 95% CI 0.12–0.39); however, data were insufficient for separate estimates of tubal-ovarian cancer risk in BRCA1 and BRCA2 subtypes.

risk-reducing bilateral prophylactic mastectomy

Prophylactic risk-reducing bilateral mastectomy is offered as a choice for women who have not been diagnosed with breast cancer. Bilateral prophylactic mastectomy in healthy BRCA mutation carriers has been demonstrated to be a very effective intervention with a 98%–99% reduction in the risk of breast cancer after a median follow-up of 4.5–6.4 years [12, 35]. In 2010, the Prevention and Observation Surgical End point (PROSE) Study Group reported a large, prospective, multicenter cohort study of 2484 women with BRCA1 or BRCA2 mutations. Patients were accrued at 22 clinical and research genetics centers in Europe and North America, from 1974 to 2008. Of the 247 women in this study who elected to undergo prophylactic mastectomy, there were no breast cancers detected compared with 7% of the women who elected not to sacrifice their breasts [33].

In addition to reflecting some self-selection mechanism (more anxious individuals would tend to choose more drastic interventions), cultural variation [36–38], incidence and mortality patterns in relatives [38, 39], marital and parity status and the manner in which the information is conveyed by the treating physician [15, 38, 40] all play roles in this delicate phase of decision making. Metcalfe et al. [9] in 2008, studied the international variation in uptake in preventative options in BRCA 1/2 carriers. Their cohort contained 1383 women without prior breast cancer, who were followed up for a median 3.9 years after genetic testing. The overall bilateral prophylactic mastectomy rate in these women was 18% (248 of 1383) and ranged from 36.3% (115 of 317) in the USA to 22.4% (88 of 393) in Canada and 6.7% (45 of 673) in Europe/Israel. Approximately half of all European patients studied were from a single institution in Poland; their decisions may not accurately reflect those of Europeans as a whole. Before proceeding with bilateral prophylactic mastectomy, the implications and risks of this procedure must be carefully discussed with patients. In a study of 609 women with a family history of breast cancer who elected to have a bilateral prophylactic mastectomy, regret was more often reported when the main reason for considering the procedure was the physician’s recommendation [41]. Furthermore, several studies have demonstrated an adverse affect on body image, femininity and sexual relationships in women choosing bilateral prophylactic mastectomy [41–46]. Decision making about prophylactic mastectomy, and other intervention strategies, and their impact on short- and long-term quality of life, remains an area of active investigation in BRCA mutation carriers.

recent improvements in surgical and reconstructive techniques

BRCA mutation carriers who undergo bilateral mastectomy have often been faced with significant morbidity and reoperation rates related to reconstruction following mastectomy for prophylaxis. In one series of 358 high-risk women (236 with a BRCA mutation) undergoing prophylactic mastectomy, 177 had no prior history of breast cancer [35]. The overall postoperative complication rate was 49.6% in women who had reconstruction, requiring further corrective surgery in the majority (71%). Recent developments in operative techniques improve the cosmetic outcome, while maintaining oncological safety and low complication rates, potentially improving the acceptability of bilateral mastectomy for healthy BRCA patients. Nipple-sparing mastectomy (NSM), although not standard in treating breast cancer, is becoming increasingly popular, especially for prophylaxis. Improvements and refinements in implant-based reconstruction have been seen in parallel. A recent series from Memorial Sloan Kettering Cancer Center reported the results of 353 NSMs in 200 patients [47]. The indication for surgery was prophylactic risk reduction in 196 (55.5%) mastectomies. A BRCA mutation was present in 22 (27.8%) of the 79 patients who had a bilateral prophylactic NSM. In this series, infection occurred in six (2%) breasts, 19.5% developed some skin desquamation which required debridement in only 12 (3.3%) and implant loss occurred in only three (1%) patients.

In summary, both prophylactic bilateral mastectomy and RRSO result in reduction of breast cancer in genetically susceptible individuals at risk of hereditary breast cancer (HBC). An in-depth discussion with the individual patient regarding the many options available is paramount in the management of mutation carriers, and requires a continual commitment by the provider to update his or her experience, while waiting for the literature to mature and generate new insights about the clinical implications of these mutations.

differences in the impact of risk-reduction strategies in BRCA1 versus BRCA2 mutation carriers

Breast cancer in BRCA2 mutation carriers tends to be estrogen receptor (ER) positive (75%) while cancers in BRCA1 mutation carriers tend to be ER receptor negative (80%) [48]. Consequently, strategies aimed at blocking estrogen hormones are expected to be more effective in reducing the risk of breast cancer in carriers of the BRCA2 mutation than in carriers of the BRCA1 mutation. Clinical data are emerging in support of this hypothesis. For instance an analysis of 19 mutation carriers included in the National Surgical Adjuvant Breast and Bowel Project P1 Breast Cancer Prevention Trial suggested a 50% risk reduction for carriers of the BRCA2 mutation but no effect for BRCA1 carriers treated with tamoxifen for chemoprevention [49]. However, these data are limited by the small number of BRCA carriers in the cohort.

In a collaboration between the PROSE study group and the Memorial Sloan Kettering Cancer Center, a study of 1079
women demonstrated a 72% reduction in the incidence of breast cancer after RRSO in BRCA2 mutation carriers (HR 0.28, 95% CI 0.08–0.92) compared with a reduction of only 49% for BRCA1 carriers (HR 0.61, 95% CI 0.30–1.22) undergoing the same procedure [10]. Predictably, RRSO reduced the risk of ER-positive but not ER-negative breast cancer in this dataset. More recently, the PROSE Study Group reported a statistically significant reduction in breast cancer risk, in patients undergoing RRSO of 64% and 37%, in BRCA2 and BRCA1 mutation carriers, respectively [33]. The effect of RRSO on breast cancer mortality was significant only for BRCA2 mutation carriers. Among the 120 BRCA2 carriers undergoing RRSO, there were no breast cancer deaths compared with 6 deaths in the BRCA2 carriers with intact ovaries. In BRCA1 mutation carriers there was a nonsignificant reduction in breast cancer-specific mortality (HR 0.3, 95% CI 0.06–1.53).

The NCCN guidelines suggest that a RRSO be carried out between the ages of 35 and 40 in BRCA gene mutation carriers [16]. The abrupt onset of menopause is well tolerated in the majority of women, but patients reporting a decline in their quality of life may need to be treated with exogenous hormones. This has led to some practitioners advocating for hysterectomy at the time of RRSO in order to allow for estrogen monotherapy [48]. However, a report from the PROSE Study Group demonstrated a similar breast cancer risk reduction after RRSO regardless of the type of hormone supplementation [50].

**breast conservation versus mastectomy in BRCA mutation carriers with breast cancer**

The incidence of IBTR and CBC have been studied extensively in BRCA mutation carriers compared with individuals with sporadic breast cancer. Liebens et al. [13] reviewed 20 studies to determine the treatment outcomes in patients with HBC. All studies analyzed were retrospective, and patients undergoing mastectomy or lumpectomy and radiation were included. They carefully considered the methodology used, the characteristics of the populations, as well as the biases and confounding risk factors. Recognizing the inevitable selection biases, the trends that emerged from the data were relatively consistent. An increased risk of IBTR in BRCA carriers was found in 5 of 17 studies and an increased risk of CBC was reported in 14 of 16 studies, as illustrated in Table 2. However, most (11 of 14) studies did not show an adverse effect on overall survival in BRCA carriers.

<table>
<thead>
<tr>
<th>Table 2. Summary of results from studies comparing breast cancer outcomes in sporadic and hereditary breast cancer</th>
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<tbody>
<tr>
<td><strong>Local recurrence</strong></td>
</tr>
<tr>
<td>No. of studies with worse outcome for BRCA+</td>
</tr>
<tr>
<td>No. of studies with same outcome</td>
</tr>
<tr>
<td>Data from [13].</td>
</tr>
</tbody>
</table>

There is much debate regarding the optimal local management of breast cancer once it is diagnosed in BRCA mutation carriers, i.e. should breast-conserving surgery with radiotherapy or a mastectomy be carried out. Breast cancer in these women is likely to be more sensitive to radiation therapy [24, 25, 51]. One concern with limited surgery followed by radiation is the in vitro hypersensitivity to radiation displayed by cells with BRCA mutations and the subsequent concern for radiation-induced complications, including second cancers [24, 51]. Several groups have examined the role of breast conservation therapy (BCT) among patients with BRCA mutations to determine whether less extensive surgery followed by radiotherapy remains a safe option. The IBTR was similar in BRCA-mutated patients when compared with sporadic breast cancer cases in four studies [52–55], as illustrated in Table 3. However, the risk of IBTR after BCT was greater in HBC in two trials [56, 57]. Perhaps IBTR may relate to the increased cancer risk conferred by genetic abnormalities in the remaining breast tissue. The choice and rationale behind performing either BCT or mastectomy must therefore be discussed carefully with BRCA patients who have been diagnosed with breast cancer.

In addition to IBTR, BRCA1 mutation carriers have demonstrated up to a 43.4% 10-year risk of CBC while patients with mutations in the BRCA2 gene have up to a 34.6% 10-year risk, as illustrated in Table 3. With a CBC risk of 3%–4% a year, it is reasonable to routinely offer the choice of surgical prophylaxis to women with a BRCA mutation diagnosed with breast cancer. Prophylactic contralateral mastectomy has been demonstrated to be very effective in reducing the risk of CBC [58–60]. However, it must be considered that the stress of a new breast cancer diagnosis often leads women to chose more extensive surgery, particularly in the absence of the appropriate psychological counseling [15, 61]. Thorough discussion and counseling should be provided for BRCA patients with breast cancer to help them through their decision-making process.

The European Institute of Oncology in Milan recently conducted a study of patients with HBC treated with BCT using a matched control design (same BCT, treatment, age, tumor size and time of surgery)[56]. The 10-year estimated cumulative incidence of IBTR was 27% for 54 mutation carriers and 4% for 162 matched controls (HR 3.9, 95% CI 1.1–13.8, P = 0.03). The 10-year cumulative incidence of CBC was 25% for mutation carriers and 1% for sporadic breast cancer patients (P = 0.03). There was a recognized selection bias, since 8 of 11 mutation carriers were referred for genetic testing at the time of IBTR (n = 6) or CBC (n = 5).

To better define the risk of IBTR in patients with HBC, Pierce et al. [14] analyzed the rates of local control and overall survival after breast conservation versus mastectomy in a cohort of 655 mutation carriers. There was a significant decrease in IBTR in the 353 patients treated with mastectomy compared with the 302 patients treated with BCT. Local failure as first site of failure was significantly more likely in the BCT population with a cumulative estimated risk at 15 years of 23.5% compared with 5.5% in the patients treated with mastectomy (P = 0.0001). The inherent limitations include the retrospective nature of this study, confounded by biases secondary to patient and physician preference for extent of surgery. As expected, the estimated 15 year cumulative risk of CBC was high, exceeding 40% in both...
groups of patients. It is encouraging that there was no statistically significant increase in CBC in the patients treated with radiation: no additional breast cancer risk from scatter radiation could be detected.

It is important to stress that overall survival, at a median follow-up of over 8 years, did not differ between the two treatment groups, despite the increased IBTR rate. Moreover, there was no difference in regional or systemic recurrences. The nature of IBTR was available for 23 of 35 patients treated with BCT in this study. The majority of these (16 of 23) were considered to be second primary tumors because they occurred in a different breast quadrant and/or had a different histology. The lack of an impact on survival corroborates this hypothesis, differentiating the effect of new tumors from those of true local recurrences, since the latter are more likely to be a predictor of systemic spread. Vigilant surveillance to allow early detection of new lesions is warranted in HBC carriers who elect to keep their breast, in order to prevent a potential detriment to overall survival from additional cancers. The American Society of Breast Surgeons recommends that this includes regular MRI screening [62].

In summary, there is an increased risk of second in-breast events in BRCA1/2 mutation carriers treated by BCT without a significant impact on the risk of systemic disease and overall survival compared with mastectomy treated patients. In addition there is a considerable risk of CBC in those with an intact contralateral breast. These findings once again illustrate the importance of discussing different surgical treatment options, not only at the time of breast cancer diagnosis, but also as a risk-reduction strategy for genetically susceptible individuals. With no overall survival advantage demonstrated with either surgical strategy, the wishes of appropriately counseled patients who want breast-conserving surgery should be respected.

**conclusions**

Women who inherit a genetic propensity for HBC, including a mutation of BRCA1 or 2 face an unenviable lifetime risk of breast and/or ovarian cancer. Early identification of an individual's BRCA mutation is crucial to optimize surveillance to allow the early detection of breast cancer if it occurs. The appropriate screening to detect breast cancer in BRCA carriers is now standardized, despite concerns about the cumulative levels of radiation exposure that it entails [19]. The recommended screening regime of mammography and breast MRI is now able to detect smaller breast cancers at earlier stages; unfortunately, this does not give a guarantee of survival. Nor does it assure patients that they will not require extensive treatments, including chemotherapy to maximize their likelihood of cure. Therefore, preventing the occurrence of cancer in BRCA carriers is important to consider at every possible opportunity. Chemoprevention with endocrine therapy, while proven in postmenopausal women is less acceptable for young healthy premenopausal BRCA carriers and its role has not been firmly established. Risk reducing salpingo-oophrectomy has two advantages; first, it drastically reduces the risk of ovarian carcinoma and secondly, it decreases the risk of breast cancer by approximately half. Consideration of RRSO is therefore recommended by professional organizations for patients between the ages of 35 and 40 years [61]. BRCA carriers who chose to undergo bilateral prophylactic mastectomy can reduce their risk of breast cancer to <1%–2% (with follow-up to date of 6.5 years). Unfortunately, both RRSO, which induces immediate menopause, and bilateral mastectomy, (despite continuing improvement in operative and reconstructive techniques) have negative impacts on quality of life, femininity and self-image in healthy asymptomatic women.

When breast cancer is diagnosed in a BRCA mutation carrier, further difficult choices and treatment decisions must be made. BCT is still an acceptable option; however, the risk of IBTR is higher than that in patients with sporadic breast cancer who undergo BCT and higher than in BRCA carriers who undergo mastectomy. The addition of a contralateral mastectomy (i.e. bilateral mastectomy) can avoid the risk of CBC which approaches 20%–40% after 10 years. Notwithstanding the increased occurrence of IBTR and CBC, a survival advantage has not been demonstrated for BRCA carriers who undergo more extensive surgery.

Despite extensive interest and numerous reported studies in BRCA mutation carriers with and without breast cancer, our available data are of limited quality. Most studies are retrospective in nature with relatively small numbers of patients and they are often biased in their patient selection and design. Increased collaboration has been seen among investigators of BRCA carriers, evidenced by recent multi-institutional reports with increasing numbers of patients [14]. This will certainly improve the quality of our knowledge and perhaps simplify the difficult decisions faced by those with an inherited predisposition for HBC.

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**Table 3.** 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></td>
<td></td>
<td></td>
<td>Genetic</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Robson et al. [55]</td>
<td>305 28</td>
<td>10</td>
<td>22</td>
<td>6.9</td>
</tr>
<tr>
<td>Haffty et al. [57]</td>
<td>127 22</td>
<td>12.7</td>
<td>49</td>
<td>21</td>
</tr>
<tr>
<td>Robson et al. [54]</td>
<td>505 56</td>
<td>9.7</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Pierce et al. [53]</td>
<td>605 160</td>
<td>7.9</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Garcia-Etienne et al. [56]</td>
<td>216 54</td>
<td>4</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td>Kirova et al. [52]</td>
<td>87 29</td>
<td>13.4</td>
<td>36</td>
<td>33</td>
</tr>
</tbody>
</table>

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[vii58] Cooper et al.
disclosure

The authors have declared no conflicts of interest.

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