Surgery and prophylactic surgery in hereditary breast cancer ☆

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ARTICLE INFO

ABSTRACT

Women with hereditary breast cancer are at increased risk of second primary cancers in the ipsilateral and contralateral breast. The level of risk varies with mutation and age at first breast cancer diagnosis. These factors as well as life expectancy should be considered when selecting the surgical approach.

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1. Introduction

Multiple prospective, randomized trials with long-term follow-up have established the equivalence of breast-conserving therapy (BCT) and mastectomy for the treatment of women with stage I and II breast cancer. Treatment selection for BCT is based upon the ability to excise the tumor to negative margins with a cosmetically acceptable result and to safely deliver radiotherapy. Over time, both contraindications to BCT [1] and rates of local recurrence (LR) have decreased [2], and BCT is now considered the preferred approach to early-stage breast cancer for the majority of women.

There is still controversy, however, regarding the use of BCT versus mastectomy in women with *BRCA1* and *BRCA2* mutations. Since the identification of the *BRCA* genes in the early 1990s, it has been recognized that *BRCA1* and *BRCA2* mutations are associated with both an extremely high risk of development of a first breast cancer, as well as a markedly elevated risk of subsequent ipsilateral and contralateral cancers. In a cohort study of 3886 women, the cumulative risk of contralateral breast cancer 20 years after a first breast cancer diagnosis was 40% (95% CI 35—45) for *BRCA1* carriers and 26% (95% CI 20—33) for *BRCA2* carriers [3]. Recognition of the high risk of bilateral cancers has led to the frequent use of bilateral mastectomies in these patients. Nevertheless, determining the appropriate surgical approach in the *BRCA* mutation carrier with unilateral carcinoma requires consideration of several questions — Is the risk of LR increased with BCT? What is the risk of contralateral cancer, and is it modified by treatment? Does contralateral prophylactic mastectomy (CPM) improve survival?

2. Local recurrence after BCT

No prospective, randomized trials have compared the outcomes in *BRCA* carriers who receive BCT versus mastectomy. This question has been addressed by retrospective comparison of the outcomes after BCT in *BRCA* mutation carriers versus those without mutations [4], as well as by comparing LR rates after mastectomy versus BCT in mutation carriers [5,6]. A 2014 meta-analysis of 10 studies (6 cohort, 4 case-control) that included 526 BRCA mutations carriers and 2320 patients with sporadic cancer reported a 17.3% (95% CI 11.4—24.2) LR rate in the *BRCA* group compared to 11.0% (95% CI 6.5—15.4; p = 0.07) in non-carriers. When studies were divided by duration of follow-up, no difference in LR was seen in studies with follow-up of <7 years (n = 1212); however, in the 1634 patients with follow-up of ≥7 years, LR occurred in 24% of *BRCA* carriers compared to 16% in sporadic cancer patients (p = 0.003) [4]. This prolonged time course is more suggestive of second primary cancers than true LR. Local recurrence is more commonly observed in the first 5—7 years post-treatment, particularly among patients with the triple-negative phenotype, which constitutes the majority of cancers in women with *BRCA1* mutations [7]. Only 2 studies, including 893 patients, attempted to distinguish between true LR and new primary cancers. In this limited dataset, no increase in the

Table 1
Local recurrence rates after BCT and mastectomy in BRCA mutation carriers.

Years after Surgery	Median % Local Recurrence (Range)			
	BCT		Mastectomy	
5	13.3% (2.0–22.0)	N = 1212	5.2% (1.4–9.0)	N = 470
10	16.2% (10.5–52.0)	N = 1566	7.3% (5.5–9.0)	N = 470
15	23.8% (15.8–49.0)	N = 1085	7.3% (5.5–9.4)	N = 470

Data from Co M. et al. [6] BCT: breast-conserving therapy.

risk of true recurrences was seen, while the relative risk of new primary carriers was increased two-fold (p = 0.05) in the *BRCA* group [4]. No significant difference in LR was observed on the basis of *BRCA1* versus *BRCA2* mutations.

Using the alternative approach of comparing outcomes in *BRCA* mutation carriers after BCT and mastectomy, Pierce et al. reported a multicenter retrospective study in which 353 BRCA carriers were treated with mastectomy (median follow-up 9 years) and 302 had BCT (median follow-up 8 years) [5]. The 5-year risk of LR was 1.4% after mastectomy and 4.1% after BCT, increasing to 4.0% and 11.0%, respectively, at 10 years, and to 5.9% and 23.5%, respectively, at 15 years (p < 0.0001). Local recurrence was noted to be significantly less common in BCT patients receiving chemotherapy. A subsequent meta-analysis published in 2019 included 16 studies examining the question of LR after BCT versus mastectomy in *BRCA* mutation carriers (Table 1) [6]. Rates of LR after BCT were higher than those observed after mastectomy at 5, 10, and 15 years of follow-up. In the mastectomy group, rates of LR increased very little after the first 5 years, consistent with what is known about the time course of LR after mastectomy in sporadic breast cancer [8]. In contrast, rates of LR after BCT continued to increase through 15 years, a pattern more consistent with second primary cancers. At 5 years of follow-up, the difference in the median rate of LR between the 2 groups was 8.1%, increasing to 16.5% by 15 years after surgery. However, this did not translate into a difference in overall survival in the 4 studies (1 prospective cohort, 2 retrospective cohorts, 1 case series) that examined this endpoint [6]. Data on breast cancer–specific survival are limited by small numbers, but no statistically significant differences based on surgical procedure have been observed [5,9,10].

Shubeck et al. reported a more contemporary series of *BRCA* carriers, 324 of whom underwent mastectomy and 100 who had BCT. Only 34% of those having BCT knew their *BRCA* status at the time of surgery. Patients having mastectomy were younger (median age 43 vs. 48 years; p = 0.001), but neither the distribution of *BRCA1* and *BRCA2* mutations nor tumor characteristics differed between the groups. The 10-year local recurrence-free survival rates were 90.3% and 94.6% for BCT and mastectomy, respectively, and in a multivariate model, surgery type was not significantly associated with LR (Shubeck S. SSO 2021). This lack of a difference in LR could be due to the more widespread use of systemic therapy in recent years, as chemotherapy was noted to significantly reduce LR in the Pierce et al. study [5], or it could be a reflection of selection bias.

Overall, the literature suggests no increase in the risk of true LR in *BRCA* mutation carriers treated with BCT, but there does appear to be an increased risk of new cancers in the conserved breast, consistent with what is known about the risk of contralateral cancer in this population.

3. Contralateral breast cancer risk

It has long been recognized that patients with *BRCA* mutations have an elevated risk of contralateral breast cancer (CBC) compared to women with sporadic breast cancer [11]. In a meta-analysis of 3970 patients from 11 retrospective studies, the risk of CBC in *BRCA* carriers with unilateral cancer was 23.7% (95% CI 17.6–30.5) compared to 6.8% (95% CI 4.2–10.0; p = 0.001) in non-carriers [4]. In the 7 studies (n = 2482 patients) that examined CBC risk in *BRCA1* versus *BRCA2* carriers, women with *BRCA1* mutations were found to have a significantly higher risk than those with *BRCA2* mutations (21.1% vs. 15.1%, respectively; p = 0.04) [4].

Recognition of the high rates of CBC has led to widespread use of bilateral mastectomy for the management of unilateral cancer in this population. However, factors that modify risk have now been identified, allowing for more individualized patient counseling. For example, age at first cancer diagnosis has emerged as an important predictor of the risk of subsequent cancer [3,12,13]. In the Graeser et al. study of 2020 BRCA mutation carriers diagnosed between 1996 and 2008, age less than 40 years at first diagnosis was significantly associated with increased CBC risk in *BRCA1* but not *BRCA2* carriers [12], and an elevated risk of CBC development in *BRCA1* compared to BRCA2 carriers was seen.

In a study by Metcalfe et al., 5 years after diagnosis, the absolute difference in CBC incidence between *BCRA1* and *BRCA2* cancers was 1.7%, and this increased to 7.6% at 15 years [13]. The differences in CBC risk based on age at first diagnosis were also noted to increase over time. At 5 years of follow-up, 14.2% of women diagnosed at <50 years of age had developed CBC compared to 8.6% of their older counterparts; by 15 years, 37.6% of those first diagnosed at <50 years had CBC compared to 16.7% of those ≥50 years at initial diagnosis [13]. These retrospective studies, as well as those included in the meta-analysis of Valachis et al. [4], are subject to significant selection bias since patients were often identified as having a *BRCA* mutation many years after their initial breast cancer diagnosis when they developed a second breast cancer.

A more accurate estimate of CBC risk comes from a prospective cohort study of *BRCA* mutation carriers recruited between 1997 and 2011 reported by Kuchenbaecker et al. The cumulative risk for CBC 20 years after a first breast cancer diagnosis was 40% for *BRCA1*, and 26% for *BRCA2* mutation carriers (hazard ratio [HR] 0.62, 95% CI 0.47–0.82; p = 0.001) [3]. In *BRCA1* carriers, the HR for CBC declined to 0.81 for those first diagnosed at age 40–50 years, and decreased further to 0.71 for those diagnosed at >50 years when compared to women with a first breast cancer before age 40 years. For *BRCA2* carriers, the HRs for CBC were 0.73 and 0.76 for those diagnosed at 40–50 years and >50 years, respectively, compared to women diagnosed before age 40 years. Some of the observed differences in the risk of CBC between *BRCA1* and *BRCA2* carriers may be due to the greater use of endocrine therapy in the *BRCA2* population; estrogen receptor–positive cancers are more common in this group, and adjuvant endocrine therapy has been shown to reduce CBC in *BRCA* carriers, as it does in sporadic cancers [14]. A multivariate analysis of factors associated with CBC risk in retrospective studies found a high level of evidence that increasing age and oophorectomy decreased CBC risk, and a moderate level of evidence of a benefit for chemotherapy and tamoxifen [4].

While there is no doubt that contralateral prophylactic mastectomy (CPM) reduces the risk of breast cancer development, its effect on survival is less clear. In a model developed by Narod et al. [15], no survival benefit from CPM was observed until 15 years after initial breast cancer diagnosis. This finding was borne out in a retrospective study of 390 BRCA mutation carriers, 209 treated by unilateral mastectomy and 181 with bilateral mastectomy. At a median follow-up of 13 years, 20% of patients had died of breast cancer. The multivariate HR for death at 20 years was 0.52 (95% CI 0.29–0.93; p = 0.03) for the CPM group; for the first 10 years after diagnosis, the HR was 0.65 (p = 0.18) and it fell to 0.20 for years 10–20 (p = 0.03) [16].

When considering the benefit of CPM, competing risks are a major consideration. In addition to the risk of death from the index cancer, women with *BRCA* mutations have a significantly elevated risk of ovarian cancer development [3]. In a study of the risk of breast cancer development in 509 *BRCA1* mutation carriers with ovarian cancer, 40% died of ovarian cancer, and 4% (n = 20) developed breast cancer. While the 10-year actuarial risk of breast cancer development was 39%, the 10-year risk conditional on survival from ovarian cancer and other causes of mortality was only 7% [17]. A Dutch case-control study found the rate of breast cancer development at 5 and 10 years after ovarian cancer to be 6% and 11%, respectively, significantly lower than the risk in *BRCA* carriers without ovarian cancer (HR 0.43, 95% CI 0.20–0.95) [18], and an additional study reported only an 11% rate of breast cancer development in ovarian cancer survivors [19]. In all these studies, breast cancer mortality was low, suggesting that prophylactic surgery is of limited benefit in this population, particularly when the risk of ovarian cancer mortality is high.

3.1. Clinical decision making

Although the risk of second primary cancers in both the ipsilateral and contralateral breast is elevated in *BRCA* mutation carriers, bilateral mastectomy is not mandatory for any patient. An effort should be made to individualize risk by considering which *BRCA* mutation is present, the age of the patient, risk of mortality from the index cancer, and the effect of therapy used for the treatment of the index cancer on the risk of subsequent cancer. An informed surgical decision can only be made if *BRCA* mutation status is known prior to surgery. While this may not be feasible in healthcare systems with limited access to timely genetic testing, in settings where such access is available, patients should be counseled that brief delays to obtain the results of genetic testing are not harmful. In patients with triple-negative cancer, if it is clear that chemotherapy will be indicated postoperatively, the use of neoadjuvant chemotherapy is an ideal approach to avoid treatment delay while allowing time for genetic counseling and testing. As illustrated in the study of Chiba et al., knowledge of mutation status prior to surgery has a dramatic effect on surgical treatment choice. Of 63 patients with unilateral breast cancer known to have a *BRCA* mutation preoperatively, 83% opted for bilateral mastectomy. In contrast, of 93 patients found to have a *BRCA* mutation after surgery, only 29% underwent an initial bilateral mastectomy. Upon learning their mutation status, half of the patients who had not initially undergone bilateral mastectomy chose to do so [20]. In patients found to have moderate penetrance genes, the risk of breast cancer development is much lower than for *BRCA* carriers, and data on the risk of second cancers are lacking, so there is much less evidence to support the use of bilateral mastectomy [21,22]. These patients should be managed in the same way as others with a similar risk of breast cancer development, such as women with atypical hyperplasia or lobular carcinoma in situ. Based on level of risk, this may include enhanced screening with magnetic resonance imaging and consideration of endocrine chemoprevention.

Counseling patients regarding the risks of nipple-sparing mastectomy (NSM) is another area where knowledge of *BRCA* mutation status is useful. This procedure requires leaving some breast tissue beneath the nipple-areolar complex in order to provide it with a blood supply, potentially increasing the risk of future breast cancers. Additionally, the exposure provided by the incisions used for NSM is more limited than what is obtained with skin-sparing mastectomy incisions, and some studies have suggested an increased risk of recurrence elsewhere on the chest wall [23]. Data on outcomes of *BRCA* mutation carriers with cancer treated with NSM are scarce. Three retrospective studies, with a total of 104

patients and follow-up times ranging from 28 to 37 months, reported only a single patient with LR. Nipple-sparing mastectomy has been used more frequently in *BRCA* patients undergoing prophylactic surgery. Jakub et al. reported 548 NSMs in 346 patients with *BRCA* mutations, with a median follow-up of 34 months for *BRCA1* carriers and 56 months for *BRCA2* carriers. No cancers have been observed to date, while 22 would have been expected with no surgery [24]. In another retrospective series of 298 NSMs in 150 patients, a single cancer was observed after a median follow-up of 33 months [25]. Overall, the short duration of follow-up in all of these studies and technical variation in the amount of breast tissue left behind make it difficult to counsel *BRCA* patients regarding the level of risk of NSM. Nevertheless, patients undertaking bilateral mastectomy to minimize the risk of future breast cancer development should be counseled that a small amount of breast tissue will be left behind beneath the nipple with the potential for future cancer development.

4. Conclusions

In the patient with unilateral breast cancer and a *BRCA* mutation, the risk of second primary cancers in the index breast and the contralateral breast is elevated. Patient, tumor, and treatment factors modify the level of risk and should be considered when discussing surgical options. While bilateral mastectomy is not mandatory for any patient subset, it offers the greatest benefit in young *BRCA1* carriers with early-stage index cancers. Patient preferences and attitudes toward risk are an important determinant of treatment choice and are informed by the results of genetic testing. Every effort should be made to obtain genetic test results prior to surgery in patients meeting the criteria for testing.

Declaration of competing interest

Monica Morrow has received speaking honoraria from Roche and Exact Sciences unrelated to the content of this manuscript.

Acknowledgments

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