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Risk of Ipsilateral and Contralateral Cancer in BRCA Mutation Carriers with Breast Cancer

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Abstract *BRCA1* and *BRCA2* mutation carriers with breast cancer have a high risk of ipsilateral breast cancer tumor recurrence (IBTR) and a high lifetime risk of contralateral breast cancer (CBC). The IBTR risk is significantly higher in women who elect breast conservation. Oophorectomy has a protective effect for both ipsilateral breast tumor recurrence and CBC. Patients with younger age of breast cancer onset have a significantly greater risk of CBC. Given the higher risk of IBTR and CBC, when indicated, patients with breast cancer should undergo genetic counseling early in their treatment course to assist them in their surgical decision-making. Knowledge of expected outcomes for *BRCA1/2* mutation carriers following breast cancer treatment can help in appropriately counseling patients and personalizing cancer therapy.

Keywords Contralateral breast cancer· BRCA1 · BRCA2 · Prophylactic mastectomy

Introduction

Women with germline *BRCA1* or *BRCA2* (*BRCA1/2*) mutations have a 55%–85% risk of developing breast cancer by age 70 [1, 2]. *BRCA1/2* mutation carriers are also at elevated risk of new breast cancers, both in the ipsilateral breast, if preserved, and in the contralateral breast. These risks, however, vary with patient characteristics such as age at breast cancer diagnosis, family history, genotype, presence or absence of oophorectomy, surgical option chosen for breast cancer treatment, and adjuvant therapy. Thus, knowledge of expected outcomes for *BRCA1/2* mutation carriers following breast cancer treatment is needed in order to appropriately council patients and personalize cancer therapy and preventive options.

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Risk of Ipsilateral Breast Cancer in BRCA Mutation Carriers

Breast-conserving therapy (BCT) consisting of breast-conserving surgery and radiation is considered the preferred option for most women with early breast cancer. However, the appropriateness of BCT in *BRCA* mutation carriers has been controversial. Haffty et al. [3] reported that at 12 years of follow-up, patients with *BRCA* mutations had significantly higher rates of ipsilateral breast tumor recurrence (IBTR) compared with patients with sporadic tumors (49% vs 21%; P=0·007). The risk of IBTR after breast conservation was also studied by Pierce et al. [4]. They compared the outcome of BCT in 160 *BRCA1/2* carriers with breast cancer compared with 445 controls. The 10- and 15-year IBTR estimates were 12% and 24%, respectively, for *BRCA* carriers and 9% and 17%, respectively, for controls; this difference was not significant. However, on multivariate analyses *BRCA1/2* mutation status was an independent predictor of IBTR in women who did not undergo an oophorectomy (hazard ratio [HR] 1.99; P=0.04). The incidence of IBTR in carriers who had undergone oophorectomy was not significantly different from that in sporadic controls (P=0.37).

Metcalfe et al. [5] also assessed the risk of IBTR in *BRCA* carriers and the effect of various treatments on this risk. The authors reported an IBTR risk of 1.2% per year,

with a 5- and 10-year actuarial risk of IBTR of 5.5% and 12.9%, respectively. The risk of IBTR was lower in women who received chemotherapy (relative risk [RR] 0.45; 95% CI, 0.24–0.84; P=0.01), radiation therapy (RR 0.28; 95% CI, 0.12–0.63), and oophorectomy (RR=0.33; 95%CI, 0.13–0.81; P=0.02).

Recently, the effect of surgical choice on ipsilateral cancer development/recurrence was assessed. Pierce et al. [6] reported the outcome of breast conservation (n=302) compared with mastectomy (n=353) in women with *BRCA1/2* mutations and breast cancer. The rate of local failure as first failure was significantly higher with BCT versus mastectomy (23.5% vs 5.5%, respectively, at 15 years; P<0.0001). Most of the local failures were felt to be second primary cancers.

Contralateral Breast Cancer in *BRCA* Mutation Carriers

Genotype, Family History, and Contralateral Breast Cancer Risk

Overall, women with breast cancer have a two- to sixfold increased lifetime risk of contralateral breast cancer (CBC) over the general population. Gao et al. [7] reported that in the SEER database, the actuarial CBC risk was 0.6% per year; at 5, 10, 15, and 20 years the risk was 3%, 6.1%, 9.1%, and 12%, respectively.

Patients with breast cancer who are from families with *BRCA1* mutations are at especially increased risk of CBC. Graeser et al. [8] performed a retrospective, multicenter cohort study comprised of 2,020 women with unilateral breast cancer from 978 families who had a *BRCA1* or *BRCA2* mutation. Relatives from families with *BRCA1* mutations were significantly younger at their first breast cancers than those from families with *BRCA2* mutations (P<0.001), and the age at contralateral breast cancer also was significantly lower in the *BRCA1* group compared with the *BRCA2* group (P<0.001). The cumulative risk for CBC 25 years after the first breast cancer was 47.4% (95% CI, 38.8%–56.0%) for patients from families with *BRCA1/2* mutations. Members of families with *BRCA1* mutations had a 1.6-fold (95% CI, 1.2-fold to 2.3-fold) higher risk of CBC than members of families with *BRCA2* mutations. The cumulative risk of having CBC up to the age of 75 years was 30.4% (95% CI, 23.9%–36.9%) in the *BRCA1* group and was 20.1% (95% CI, 12.1%–28.1%) in the *BRCA2* group.

Malone et al. [9] recently conducted a nested case-control study comparing patients with CBC diagnosed 1 year or more after a first primary breast cancer (n=705) and controls with unilateral breast cancer(n=1,398) who were ascertained from an underlying population-based cohort of 52,536 women diagnosed with a first invasive breast cancer before age 55 years. Compared with non-carriers of mutations in either gene, *BRCA1* and *BRCA2* mutation carriers had 4.5-fold (95% CI, 2.8- to 7.1-fold) and 3.4-fold (95% CI, 2.0- to 5.8-fold) increase risk of CBC, respectively. Metcalfe et al. [10] recently reported that the actuarial 15-year risk of CBC is 36.1% for women with *BRCA1* mutations and 28.5% for women with *BRCA2* mutations; this difference was not statistically significant.

Metcalfe et al. [10] reported that for women <50 years of age, the family history was significantly associated with CBC risk; women with two or more first-degree relatives with breast cancer were at higher risk of CBC compared with women with only one first-degree relative or no first-degree relatives with breast cancer (50% vs 36%, P=0.0005). Thus, in younger women family history may give insight into which *BRCA* mutations themselves are more penetrant or into genetic modifiers of risk within families.

It is likely that variations in other genes will alter the likelihood a *BRCA* carrier will develop breast cancer or CBC. In the Women's Environment, Cancer and Radiation Epidemiology (WECARE) study, the *BRCA1/2* status was assessed in 632 white women with asynchronous contralateral breast cancer and 1,221 women with unilateral breast cancer [11]. This was a population-based, multi-center study of asynchronous contralateral breast cancer. In this study, among *BRCA1* carriers, two single nucleotide polymorphisms (SNPs) of *BRCA2* were significantly associated with the risk of CBC. BRCA2-rs2061154 was associated with a decreased risk of CBC (odds ratio [OR] 0.41; 95% CI, 0.19–0.87), and BRCA2-rs206117 was associated with an increased risk of CBC (OR 2.26; 95% CI, 1.10–5.48). Over the next decade, as in depth molecular profiling becomes increasingly more available, additional genotypes that modify the risk of CBC in BRCA mutation carriers is likely to surface.

Age at Diagnosis and CBC Risk

Malone et al. [9] demonstrated that the relative risk of CBC for *BRCA* mutation carriers increased as age of first diagnosis decreased. In *BRCA1/2* mutation carriers, for patients diagnosed between 25 and 54 years of age, the overall CBC risk at 10 years was 18.4% (95% CI, 16.0–21.3). The 10-year CBC risk for patients diagnosed between ages 30 and 34 years was 30.7%, for patients diagnosed between ages 40 and 44 years the risk was 19.4%, and for those diagnosed between ages 50 and 54 years the risk was 10.8%. Similarly, Metcalfe et al. [10] reported that the risk of CBC was significantly lower in *BRCA* mutation carriers who developed breast cancer at age 50 years or later compared with women who developed

breast cancer before 40 years of age (RR 0.47; 95% CI, 0.47–0.82; P=0.008). The cumulative risk of CBC at 5, 10, and 15 years was 14.2%, 23.9%, and 37.6%, respectively, for women younger than 50 years of age at diagnosis, and was 8.6%, 14.7%, and 16.8%, respectively, for women older than 50 years of age at diagnosis [10].

Oophorectomy

As seen with IBTR rates, oophorectomy also has a significant impact on the risk of CBC. Metcalfe et al. [10] reported that of 810 patients in their series, 489 (60.4%) underwent an oophorectomy. Patients who underwent an oophorectomy had a significantly lower CBC risk (RR 0.48; 95% CI, 0.27–0.82; P= 0.0006). The risk reduction was significant for women diagnosed with their first cancer before the age of 50 years, but not for those older than 50 years of age. Oophorectomy was associated with a significant reduction in *BRCA1* mutation carriers (RR 0.48; 95% CI, 0.27–0.84; P=0.01). Oophorectomy was associated with a 51% lower risk of CBC in *BRCA2* carriers, but this difference did not achieve statistical significance (P=0.11)

Systemic Therapy and Radiation Therapy

Reding et al. [12] assessed the effect of systemic therapy on CBC risk in the WECARE study. Chemotherapy was associated with lower CBC risk in both non-carriers (RR 0.6; 95% CI, 0.5–0.7) and carriers (RR 0.5; 95% CI, 0.2–1.0). Tamoxifen was associated with a significant reduction in CBC risk in non-carriers (RR 0.7; 95% CI, 0.6–1.0; P=0.03). The reduction in CBC seen with tamoxifen in mutation carriers did not reach significance (RR 0.7; 95% CI, 0.3–1.8).

Gronwald et al. [13] studied 285 women with bilateral breast cancer and a *BRCA1/2* mutation and 751 control women with unilateral breast cancer and a *BRCA1/2* mutation in a matched case-control study. The history of tamoxifen use for treating the first breast cancer was compared between the groups. The multivariate odds ratio for CBC associated with tamoxifen use was 0.50 for *BRCA1* carriers (95% CI, 0.30–0.85) and was 0.42 for *BRCA2* carriers (95% CI, 0.17–1.02). The protective effect of tamoxifen was not seen among women who had undergone an oophorectomy. Recently, Metcalfe et al. [10] also assessed the effect of tamoxifen on CBC risk. In that study, no significant reduction of CBC risk with tamoxifen was observed; however, 60% of the patients in the study had undergone an oophorectomy.

There have been concerns that radiation therapy may increase the CBC risk. Pierce et al. [6] reported that when the cumulative incidence estimates for developing CBC were analyzed by the use of adjuvant radiation therapy for the ipsilateral breast cancer, the results did not demonstrate a significant difference (P=0.44), suggesting no increase in CBC from scatter radiation therapy.

Surgical Implications

Taken together, these studies demonstrate that for a young woman who is a *BRCA* mutation carrier and has breast cancer, bilateral mastectomy is likely to maximally decrease the risk of new primary tumors in both breasts. In a well-informed patient who strongly desires unilateral BCT, this could be pursued. However, both breasts need to be closely followed with clinical exams, as well as mammography alternating with MRI. This option may be most acceptable in patients who have a breast cancer diagnosis at an older age or in patients who have undergone an oophorectomy.

Given that *BRCA* mutation status is a significant risk factor for IBTR and CBC, it is important to consider genetic counseling for newly diagnosed breast cancer patients who are at high risk of being a *BRCA* mutation carrier. Patients who have a breast cancer diagnosis at age less than 50 years, those with ipsilateral multicentric or bilateral cancers, or male breast cancer should be considered for genetic counseling. Breast cancer patients from families with individuals known to be *BRCA* mutation carriers and patients with a family history of early breast cancer or with ovarian cancer should also be considered for genetic counseling. In considering the family history, the number of non-affected relatives and family history of *BRCA*-associated related cancers, such as pancreas and prostate cancer, should be considered. Ethnicity, such as Ashkenazi Jewish background, should be considered. The tumor histology (medullary cancer) and subtype (triple-negative breast cancer) are additional variables that are associated with the risk of being a *BRCA* mutation carrier [14, 15].

There is an increasing interest in *c*ontralateral prophylactic mastectomy (CPM) for risk reduction among breast cancer patients [16, 17]. The absolute CBC risk and the absolute risk reduction that will be obtained needs to be discussed with patients to facilitate informed decision-making. Non-oncologic issues such as breast symmetry and reconstructive options should be taken into consideration as well. In addition, patient comorbidities and the competing risk conferred by the ipsilateral breast cancer being treated also need to be considered. CPM would be expected to offer the greatest benefit for young women with *BRCA*-associated early-stage breast cancer [18].

In a recent study, Yi et al. [19] showed that of 1,223 patients who underwent mastectomy between the years 2000 and 2006 at MD Anderson Cancer Center, 284

(23.2%) underwent immediate or delayed CPM. On multivariable analysis, family history of breast cancer, *BRCA1/2* mutation testing, as well as age <50 years, white ethnicity, lobular histology, clinical stage, and use of reconstruction were associated with the use of CPM. Surprisingly, only 1.3% of patients underwent genetic testing before surgery, with testing increasing in later years. It is likely that a more contemporary series would show greater pre-surgical testing. Genetic risk assessment is an important tool that can help stratify patients based on their risk of CBC in order to determine the absolute expected benefit from CPM.

Initiation of genetic counseling at presentation is preferable as it assists in surgical planning and patient decision-making. It also ensures that genetic counseling actually gets done. However, genetic counseling at the time of diagnosis of a new breast cancer is made more challenging due to the patient's anxiety surrounding the cancer diagnosis. The behavioral and psychosocial effects of rapid genetic testing are currently being tested in a randomized clinical trial in the Netherlands (http://www.clinicaltrials.gov NCT00783822).

Patients who are eligible for or interested in BCT but are considering bilateral mastectomy if they are *BRCA* mutation carriers can either defer surgery for a few weeks to allow for testing or can proceed with surgery and testing simultaneously. The advantage of proceeding with surgery is that it will allow assessment of nodal status and determine need for postmastectomy radiation (PMRT), an important consideration in reconstructive planning. The disadvantage is mainly cosmetic, with breach of skin envelopment, often through a different incision than would have been chosen for cosmetic purposes. However, if surgical treatment is pursued in parallel with genetic testing, it is important to get genetic testing results back before radiation therapy is initiated to ensure that patients who do not need PMRT are spared radiation therapy. Patients who need or elect ipsilateral mastectomy for their treatment and do not need PMRT can be offered simultaneous bilateral skin-sparing mastectomy and reconstruction. Patients who need PMRT with delayed autologous reconstruction can undergo bilateral mastectomy at first surgery or can delay CPM until definitive ipsilateral reconstruction, with the recognition of the possibility of an interim breast cancer.

Conclusions

BRCA1 and *BRCA2* mutation carriers with breast cancer have a high risk of IBTR and a high lifetime risk of CBC. The IBTR risk is significantly higher in women who elect breast conservation compared with mastectomy. Oophorectomy has a protective effect for both IBTR and CBC. Patients with younger age of breast cancer onset have significantly greater risk of CBC. Given the higher risk of IBTR and CBC, when indicated, patients with breast cancer should undergo genetic counseling early in their treatment course to assist in their surgical decision-making. Knowledge of expected outcomes for *BRCA1/2* mutation carriers following breast cancer treatment can help appropriately council patients and personalize cancer therapy. For patients that forego bilateral mastectomy, close surveillance is recommended.

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