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BRCA Mutation Testing in Determining Breast Cancer Therapy

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Abstract

BRCA-mutation associated breast cancer differs from sporadic breast cancer with regard to future cancer risks and sensitivity to systemic therapies. Now that rapid genetic testing for *BRCA1* and *BRCA2* mutations is available at the time of breast cancer diagnosis, *BRCA* mutation status can be considered when making treatment and prevention decisions for *BRCA* mutation carriers with breast cancer. This article reviews surgical options for management of affected *BRCA* mutation carriers with emphasis on the risks of ipsilateral recurrence and contralateral breast cancer. The roles of breast conserving surgery, prophylactic mastectomy and oophorectomy are reviewed. In addition, sensitivity of *BRCA* mutation-associated breast cancer to endocrine therapy, platinum chemotherapy and poly (ADP-Ribose) polymerase inhibitors is reviewed.

Keywords

BRCA1; BRCA2; Breast cancer; Treatment

Only 5–10% of breast cancer cases are hereditary, however, for women with germline *BRCA* mutations, the breast cancer risk is substantial. Estimates have varied, but a recent meta-analysis reported cumulative breast cancer risks by age 70 for *BRCA1* and *BRCA2* mutation carriers to be 57% and 49% respectively (1, 2). Women with *BRCA* mutation-associated breast cancer also face elevated risk of second malignancies. The 10-year risk of ovarian cancer has been reported to be 12.7% and 6.8% for women with *BRCA1* and *BRCA2* mutation-associated breast cancer respectively (3). Studies have also consistently identified an elevated risk of contralateral breast cancer in *BRCA* mutation carriers. In contrast, reports regarding whether the risk of ipsilateral recurrence is higher in women with *BRCA* mutation-associated breast cancer than in women with sporadic breast cancer have conflicted (4, 5)

In addition to the elevated risk of second cancers, several other unique characteristics of *BRCA* mutation-associated breast cancer have recently been identified. When compared to sporadic breast cancers, *BRCA1* mutation-associated breast cancers are more likely to be

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triple negative while those associated with *BRCA2* mutations are more likely to be estrogen receptor positive (6, 7). Reports regarding prognosis have conflicted over time, and at present do not indicate that *BRCA* mutation status is an independent prognostic factor (5). Recent research, however, suggests unique sensitivity and resistance of *BRCA* mutation-associated breast cancers to specific systemic therapies (8, 9).

Until recently, the management of *BRCA* mutation-associated breast cancer did not necessarily differ from the management of sporadic breast cancer. However, consideration of the future cancer risks faced by this population, new data regarding unique sensitivity to systemic therapies and the availability of *BRCA* mutation testing at the time of breast cancer diagnosis are changing this paradigm. This review discusses recent advances in the use of *BRCA* mutation testing at the time of breast cancer diagnosis and the incorporation of test results into the complex treatment and prevention decisions required for *BRCA* mutation carriers with breast cancer.

Feasibility of Rapid Genetic Counseling and *BRCA1/2* Mutation Testing at the Time of Breast Cancer Diagnosis

Traditionally, genetic counseling and *BRCA1/2* mutation testing has been performed after the completion of primary surgery for breast cancer. Once test results become available, many women found to have deleterious *BRCA* mutations choose to undergo a second breast surgery or bilateral salpingo-oophorectomy for risk reduction (10, 11). Rapid turnaround of *BRCA1/2* mutation tests has recently become available, allowing patients to undergo genetic testing at the time of breast cancer diagnosis without delaying treatment and to therefore incorporate test results into management decisions. This may obviate the need for a second breast surgery for risk reduction, as some women found to have deleterious mutations choose to simultaneously undergo therapeutic surgery for the affected breast and risk reducing surgery for the contralateral breast.

Reports from a number of different countries suggest that *BRCA* testing at the time of breast cancer diagnosis is feasible and that it often impacts surgical decisions. Studies indicate that women who test positive for deleterious mutations are more likely to undergo bilateral mastectomies than breast conserving surgery, with reported rates of bilateral mastectomy among mutation carriers identified at the time of breast cancer diagnosis ranging from 48–100% (12–17).

When performed according to the routine schedule, *BRCA* mutation testing has not been associated with increased distress in breast cancer patients; however distress associated with testing in the peri-diagnostic setting has not yet been extensively studied. A report of 149 women who underwent peri-diagnostic genetic testing found no differences in quality of life or distress one year after testing among those women who underwent mastectomy of the affected breast plus contralateral prophylactic mastectomy and those who underwent unilateral mastectomy or breast conserving surgery (18). Further studies regarding the psychosocial impact of peri-diagnostic testing will be important since the period surrounding a breast cancer diagnosis is already a stressful time.

At the present, there are no formal guidelines stating which patients should be referred for genetic risk evaluation at the time of breast cancer diagnosis, however standard criteria for referral for genetic risk evaluation have been applied to this population (19). In general, women with at least a 10% likelihood of carrying a *BRCA* mutation have been included in studies of peri-diagnostic genetic testing to date (12, 18, 20, 21). Certainly, high risk women for whom surgical treatment decisions could be impacted by genetic test results should be considered for peri-diagnostic genetic risk evaluation. To date, data regarding the impact of

peri-diagnostic genetic risk evaluation on breast cancer therapy is limited to retrospective and non-randomized prospective studies, however randomized trials evaluating the impact of peri-diagnostic genetic risk evaluation in comparison to standard genetic risk evaluation on breast cancer surgical procedure and psychosocial outcomes are ongoing (21, 22).

Impact of *BRCA* Mutation Status on Local Therapy for Breast Cancer

When considering options for local therapy for *BRCA* mutation-associated breast cancer, several issues come into play. Questions arise about the efficacy of breast conserving therapy and the possibility of excess toxicity of radiation in mutation carriers. Additionally, given the high rate of contralateral breast cancer, mutation carriers with newly diagnosed breast cancer may choose to incorporate breast cancer prevention into their surgical management and undergo mastectomy for the affected side plus contralateral prophylactic mastectomy. This section reviews issues related to management of the affected breast and options for the contralateral breast.

Ipsilateral Recurrence Risk after Breast Conservation for BRCA Mutation-Associated Breast Cancer

Estimates of the risk of ipsilateral recurrence after breast conserving therapy in women with *BRCA* mutation-associated breast cancer have varied over time. Most recent studies suggest that the risk of ipsilateral breast tumor recurrence after breast conserving surgery and radiation is not significantly different in women with *BRCA* mutation-associated breast cancer than in women with sporadic breast cancer (4, 5, 23). However, many studies are limited by short follow-up and studies with 10–15 year follow-up have revealed a trend towards higher risk of ipsilateral recurrence in *BRCA* mutation carriers than sporadic controls (5, 24, 25). Of note, the ipsilateral recurrences in *BRCA* mutation carriers typically occur more than 5 years after the index cancers, often occur in separate quadrants of the breast and often have different histologic patterns, suggesting that they represent new primary cancers rather than true in-breast recurrences (26, 27).

The risk of ipsilateral recurrence after breast conserving therapy for *BRCA* mutation-associated breast cancer may be modulated by several factors such as patient age, use of tamoxifen, chemotherapy, and oophorectomy (Table). Studies assessing the impact of these factors however have been limited by methodological issues and small numbers, making definitive conclusions difficult to draw. Several investigators have identified age < 50 years at diagnosis of the index breast cancer as a risk factor for ipsilateral recurrence (23–25). Oophorectomy, adjuvant tamoxifen and adjuvant chemotherapy have all been reported to reduce the risk of ipsilateral recurrence, but the degree of risk reduction achieved by each of these interventions individually has been difficult to assess (24, 26, 27). In particular, it has been difficult to isolate any potential reduction in the risk of ipsilateral recurrence from oophorectomy from that due to chemotherapy-induced amenorrhea (27). And, it is uncertain whether any reduction in the risk of ipsilateral recurrence associated with tamoxifen use is limited to women who do not undergo oophorectomy or whether it is additive to the benefits of oophorectomy in this population (24, 26).

In a prospective study of 396 women with hereditary breast cancer managed with breast conservation, Metcalfe observed a 55% reduction in the risk of ipsilateral recurrence with adjuvant chemotherapy, a 67% reduction in the risk of ipsilateral recurrence with oophorectomy but no impact of tamoxifen on the risk of ipsilateral recurrence (26). In contrast, in Pierce's retrospective cohort study comparing 160 women with *BRCA* mutation-associated breast cancer and 445 patients with sporadic breast cancer all managed with breast conservation, tamoxifen was associated with a 58% reduction in the risk of ipsilateral recurrence independent of mutation status. In this study, the 15-year risk of ipsilateral

recurrence did not differ between the hereditary and sporadic groups as a whole (24% and 17% respectively, p=0.19), but the risk of ipsilateral recurrence was higher in the hereditary group when carriers who underwent oophorectomy were excluded from the analysis. This finding supports the notion that oophorectomy reduces the risk of ipsilateral recurrence in *BRCA* mutation carriers managed with breast conservation (24). However, in a subsequent study comparing women with *BRCA* mutation-associated breast cancer who underwent breast conservation to those who underwent mastectomy, Pierce did not observe a reduction in the risk of ipsilateral recurrence in the breast conservation group with oophorectomy. This study, however, revealed a benefit of adjuvant chemotherapy in reducing the risk of ipsilateral recurrence in *BRCA* mutation carriers who underwent breast conserving therapy (27).

Some have suggested that the reason breast conservation is not associated with an overall increased risk of early ipsilateral recurrence in *BRCA* mutation carriers compared to sporadic controls is that radiation may eradicate any preclinical second primary malignancies within the breast, thereby preventing or delaying their presentation as metachronous ipsilateral recurrences (28). In the past, there was concern that *BRCA* mutation carriers undergoing radiation as a component of breast conserving therapy may experience enhanced radiation-associated toxicity due to impaired ability to repair radiation-induced DNA breaks. However, Pierce identified no increase in acute or chronic morbidity in the skin, subcutaneous tissue, bone or lung in *BRCA* mutation carriers undergoing radiation as a component of breast conserving therapy (24).

In summary, breast conserving surgery or mastectomy are appropriate treatment options for *BRCA* mutation-associated breast cancer. Maneuvers which result in decreased estrogen exposure such as tamoxifen or oophorectomy in premenopausal women, appear to reduce the risk of ipsilateral recurrence and new metachronous ipsilateral primary breast cancer in affected *BRCA* mutation carriers managed with breast conservation. Additionally, adjuvant chemotherapy and radiation therapy, likely through treatment of preclinical second primary breast cancer, also result in reduced risk of future ipsilateral breast cancer events. What remains unclear is the relative and additive effects of these various modalities on the risk of ipsilateral recurrence after breast conservation for *BRCA* mutation-associated breast cancer.

Contralateral Breast Cancer Risk and the Role of Prophylactic Contralateral Mastectomy for BRCA Mutation-Associated Breast Cancer

Studies have consistently demonstrated a substantial risk of metachronous contralateral breast cancer among *BRCA* mutation carriers who retain contralateral breast tissue after a diagnosis of primary breast cancer. Most studies have revealed 10-year estimates of contralateral breast cancer risk of approximately 15–40%, with an estimated yearly risk of 3% (4, 5, 29, 30). In comparison to the substantial risk of contralateral breast cancer faced by women with *BRCA* mutation-associated breast cancer, the risk of metachronous contralateral breast cancer in women with sporadic breast cancer is estimated to be approximately 3–10% (24, 25, 30, 31).

Similar to the risk of ipsilateral breast cancer recurrence, the risk of contralateral breast cancer in *BRCA* mutation carriers is modulated by several factors (Table). The risk of contralateral breast cancer is 1.5-fold higher in *BRCA1* mutation carriers than in *BRCA2* mutation carriers (27, 29). Young age at diagnosis, especially in *BRCA1* mutation carriers, has been associated with an increased risk of contralateral breast cancer (26, 29, 30). In a nested case-control study of 705 cases with contralateral breast cancer and 1,398 controls with unilateral breast cancer, Malone observed a decrease in the risk of contralateral breast cancer as age of diagnosis increased among *BRCA1* mutation carriers (30). Similarly, in a retrospective, multi-center cohort study of 2,020 women with unilateral hereditary breast

cancer, Graeser observed an association between younger age at diagnosis of the index cancer and increased risk of contralateral breast cancer among *BRCA1* mutation carriers, however this association was not statistically significant among *BRCA2* mutation carriers (29).

The impact of other cancer therapies on the risk of contralateral breast cancer in *BRCA* mutation carriers is controversial. In general, the proportional reductions in the risk of contralateral breast cancer associated with other cancer treatments are thought to be similar for *BRCA* mutation-associated and sporadic breast cancer, but the potential absolute benefits may be greater in *BRCA* mutation carriers due to their higher risk of contralateral breast cancer (32). Similar to the situation with regard to the risk of ipsilateral breast recurrence, it is difficult to disentangle the effects of adjuvant tamoxifen, oophorectomy and adjuvant chemotherapy on the risk of contralateral breast cancer in women with *BRCA* mutation-associated breast cancer. Some studies have reported a 50–60% reduction in the risk of contralateral breast cancer with adjuvant chemotherapy, regardless of whether oophorectomy is performed (32, 33). However, other studies have shown no impact of adjuvant chemotherapy on the risk of contralateral breast cancer (28, 30, 34). Some studies have reported that tamoxifen reduces the risk of contralateral breast cancer by approximately 50–70% in *BRCA* mutation carriers, although this may be limited to women who do not undergo oophorectomy (24, 33, 35). In contrast, other studies have not reported a significant reduction in the risk of contralateral breast cancer associated with tamoxifen in *BRCA* mutation carriers, especially after adjustment for other variables (28, 30, 32, 34, 36). Most studies have reported that oophorectomy reduces the risk of contralateral breast cancer in *BRCA* mutation carriers by approximately 50–70%, with the greatest benefit seen if the diagnosis of the index cancer occurs prior to the age of 50 (24, 26, 33, 34). Additionally, Pierce's study comparing mutation carriers undergoing breast conservation to those undergoing mastectomy did not reveal greater risk of contralateral breast cancer in the breast conservation group, suggesting no increased risk of contralateral disease due to radiation scatter (27).

Given the substantial risk of contralateral breast cancer and the uncertain benefits of other treatment modalities in reducing this risk, some women with *BRCA* mutation-associated breast cancer undergo contralateral prophylactic mastectomy. Among *BRCA* mutation carriers with breast cancer, this procedure has been reported to reduce the risk of future contralateral breast cancer by at least 90% (37, 38). This degree of risk reduction is similar to the reduction in the risk of breast cancer reported among unaffected *BRCA* mutation carriers who undergo bilateral prophylactic mastectomy (38–41). Despite the significant reduction in the risk of contralateral breast cancer associated with prophylactic contralateral mastectomy in *BRCA* mutation carriers, the procedure has not to date been found to improve survival, although studies have been limited by short follow-up (37, 38, 42).

Women with *BRCA* mutations who opt for contralateral prophylactic mastectomy are also more likely to undergo oophorectomy. The reduction in the risk of contralateral breast cancer associated with contralateral prophylactic mastectomy in this population is independent of whether oophorectomy is performed and the risk of contralateral breast cancer in women with *BRCA* mutations who undergo both procedures has been reported to be less than 2% (37, 42, 43). Women with *BRCA* mutation-associated breast cancer who undergo contralateral prophylactic mastectomy are, not surprisingly, also more likely to undergo mastectomy than breast conserving therapy for the affected breast (43). In addition, other factors associated with the choice to undergo contralateral prophylactic mastectomy in *BRCA* mutation carriers include young age, residing in the United States and experiencing high cancer-specific distress (43, 44).

Overall, surveys indicate that women who choose contralateral prophylactic mastectomy are usually satisfied with their choice and do not experience a reduction in quality of life after the procedure (18, 45, 46). However, some women experience regret after prophylactic mastectomy. Reported reasons for regret include poor cosmetic result, reduced sense of sexuality and lack of education about the efficacy of contralateral prophylactic surgery and screening (47).

In sum, either breast conserving therapy for the affected breast or mastectomy for the affected breast performed either with or without contralateral prophylactic mastectomy are appropriate options for the surgical management of women with *BRCA* mutation-associated breast cancer. While breast conservation is safe in the short term, women who choose this option must accept the risks of contralateral new primary breast cancer and late ipsilateral recurrences/new primary breast cancers. In order to detect these subsequent breast cancers, it is recommended that women who retain breast tissue undergo enhanced surveillance with magnetic resonance imaging in addition to mammography (19).

Impact of *BRCA* Mutation Status on Systemic Therapy for Breast Cancer

Traditionally, decisions regarding systemic therapy for *BRCA* mutation-associated breast cancer have been made based on the characteristics of the disease and not on the *BRCA* mutation status. However, this may change as questions exist regarding the impact of mutation status on prognosis and recent data suggesting unique patterns of sensitivity and resistance to systemic therapies in *BRCA* mutation-associated breast cancer emerges (48–52). Notably, *BRCA* mutation-associated breast cancers appear to be particularly sensitive to a new class of drugs which inhibit poly (ADP-Ribose) polymerase (PARP) (52–55). Based on this data, *BRCA* mutation status may soon become relevant to decisions regarding systemic therapy for *BRCA* mutation-associated breast cancer.

BRCA Mutation Status as a Prognostic Factor

When compared to sporadic breast cancers, *BRCA1* mutation-associated breast cancers have a more aggressive phenotype and are typically high grade, estrogen receptor negative, progesterone receptor negative and HER2 negative (6, 7, 56). In contrast, *BRCA2* mutation-associated breast cancers are more similar to sporadic breast cancer, although they are more likely to be estrogen receptor positive (6, 7, 56, 57).

A number of studies have evaluated whether *BRCA* mutation status independently impacts breast cancer prognosis. Many of these studies have been hampered by small sample size, survival bias, and incomplete data regarding tumor and treatment characteristics. In an attempt to overcome survival bias, two studies have performed testing for *BRCA* founder mutations on tumor blocks obtained from consecutively diagnosed breast cancer patients of Ashkenazi Jewish descent (36, 56). In the first study, 10-year breast cancer-specific survival was significantly worse in *BRCA1* mutation carriers than non-carriers (62% versus 86%, $p < 0.001$), but not in those with *BRCA2* mutations compared to non-carriers (84% versus 86%, $p=0.76$). However, in this study, *BRCA1* mutation status was predictive of worse outcome only in those who did not receive chemotherapy (36). In the second study, no difference in 10-year survival rate was seen between *BRCA1*mutation carriers, *BRCA2* mutation carriers, and non-carriers (56). The interpretation of the above studies is hampered by the lack of data on some other well-recognized prognostic factors such as tumor grade and hormone receptor status.

In a study from the high risk clinic at Rotterdam, the prognosis of 223 patients with *BRCA1* mutation-associated breast cancer was compared to that of 446 controls with sporadic breast cancer matched for age and year of diagnosis. On multivariate analysis, no difference in

breast cancer-specific survival was seen between the *BRCA1* mutation carriers and sporadic controls (HR = 1.29, 95% CI 0.85–1.97) (58). In a subsequent analysis from the same group, no difference in overall survival was noted for *BRCA2* mutation-associated breast cancers compared to sporadic controls (7). Based on these studies, *BRCA* mutation status should not currently be viewed as an independent predictor of clinical outcome for breast cancer.

Chemotherapy

The protein products of the *BRCA1* and *BRCA2* genes are involved in the cellular responses to DNA damage induced by various chemotherapy agents. As a result, *BRCA* functional status is thought to impact sensitivity to chemotherapy (53, 54, 59). Indeed, substantial laboratory data suggests that *BRCA1*-defective cell lines have enhanced sensitivity to DNA damaging chemotherapy, such as platinums, and relative resistance to microtubule interfering chemotherapy, such as taxanes, when compared to *BRCA*-competent cell lines (59–61).

In the clinical setting, trials assessing response to neoadjuvant chemotherapy have proven useful for determining the impact of *BRCA* mutation status on chemotherapy response or resistance. Several small recent studies support the laboratory findings described above, demonstrating enhanced responses to platinums and suggesting reduced responses to taxanes in the neoadjuvant treatment of *BRCA* mutation-associated breast cancer (48–50). However, a recent study from MD Anderson demonstrated that *BRCA1* carriers had a high pathological complete response (pCR) to neo-adjuvant anthracyline-taxane based chemotherapy (pCR BRCA1 carrier 46% vs 22% in noncarriers) (62). In this study, *BRCA* status and ER negativity were independently associated with higher pCR rates, suggesting that it is premature to conclude that standard therapy with taxane containing regimens are inferior in carriers. Of note, a remarkable pathologic complete response rate exceeding 80% has been reported in a small prospective trial evaluating neoadjuvant cisplatin in *BRCA1* mutation-associated breast cancer (48).

Outside of the neoadjuvant setting, there is little clinical data regarding chemotherapy for *BRCA* mutation-associated breast cancer. As reviewed above, standard adjuvant chemotherapy may reduce the risk of ipsilateral recurrence in *BRCA* mutation-associated breast cancer treated with breast conserving therapy, although the impact of standard adjuvant chemotherapy on the risk of future contralateral breast cancer is more controversial (26–28, 30, 32, 34).

With regard to the survival benefit associated with standard adjuvant chemotherapy, studies have suggested that chemotherapy may mitigate any negative prognosis associated with *BRCA1* mutation status. As stated above, in the retrospective cohort study in which testing for *BRCA* founder mutations was performed on consecutively diagnosed Askhenazi Jewish women, Robson reported inferior breast cancer-specific survival among *BRCA1* mutation carriers. However, this effect was mitigated by chemotherapy, and *BRCA1* mutation status was only a predictor for breast cancer mortality among patients who did not receive adjuvant chemotherapy (36). Similarly, in Rennert's study described above in which *BRCA* mutation testing was performed on consecutively diagnosed Israeli breast cancer patients, there was no overall difference in survival based on mutation status. However, consistent with Robson's findings, Rennert identified a non-statistically significant trend towards improved survival with the use of adjuvant chemotherapy in *BRCA1* mutation carriers. Among women who received chemotherapy, 10-year survival rates were 71% for *BRCA1* mutation carriers and 46% for sporadic controls (HR = 0.48, 95% CI 0.19–1.21, p = 0.12) and the interaction term between *BRCA1* mutation status and chemotherapy was significant for overall survival (p=.02) (56). These findings suggest enhanced benefit from adjuvant chemotherapy in *BRCA1* mutation-associated breast cancer (36, 56).

In the metastatic setting, a small case control study revealed a lower response rate and shorter time to progression with palliative taxane therapy in hormone receptor negative *BRCA1* mutation-associated breast cancer when compared to hormone receptor negative sporadic breast cancer controls, consistent with the theory of relative resistance of *BRCA* mutation-associated breast cancer to anti-microtubule agents (63). In addition, the promising neoadjuvant data regarding cisplatin has spurred a randomized phase III trial comparing carboplatin to docetaxel in metastatic *BRCA* mutation-associated breast cancer (NCT00321633) and a smaller phase II trial evaluating cisplatin for metastatic *BRCA1* mutation-associated breast cancer. Early results from the phase II trial have been encouraging, with 46% of women achieving a complete response and 26% of women achieving a partial response (64).

PARP Inhibitors

Perhaps the most promising recent development in systemic therapy for *BRCA* mutation-associated breast cancer is PARP inhibitors. PARP1 is an enzyme involved in the repair of single strand DNA breaks via the process of base excision repair (BER). In the absence of PARP1-mediated repair activity, single strand DNA breaks degenerate into double strand DNA breaks which are repaired via the process of homologous recombination (HR), a process dependent on the protein products of the *BRCA1* and *BRCA2* genes. In this redundant system, a deficiency in BER can be compensated for by HR in the presence of intact *BRCA* function. However, cancer cells occurring in *BRCA* mutation carriers are deficient in their ability to repair DNA via HR. Thus, if PARP1 is inhibited in cancer cells in *BRCA* mutation carriers, single strand DNA breaks cannot be repaired via BER and degenerate into double strand DNA breaks which also cannot be repaired by HR, resulting in cell death. This relationship between the *PARP1* and *BRCA1/2* genes is considered a “synthetic lethal” relationship, as a deficiency in one gene product alone is not lethal, but a deficiency in both results in cell death. Based on this relationship, PARP inhibitors are proving to be particularly effective in *BRCA* mutation-associated cancers but relatively non-toxic to cells with an intact HR pathway (53–55).

Although no PARP inhibitors have yet been approved by the Food and Drug Administration, a growing body of pre-clinical and clinical data supports efficacy of PARP inhibitors in *BRCA* mutation-associated cancers. In the laboratory setting, enhanced cell death via PARP inhibition has been observed in cell line and xenograft models lacking *BRCA* function (65–70).

Clinical trials of PARP inhibitors to date have primarily been performed in patients with *BRCA* mutation-associated cancers. However, since triple negative breast cancers often have a functional deficiency in BRCA even in the absence of a germline *BRCA* mutation, some trials have included triple negative breast cancer in addition to *BRCA* mutation-associated breast cancer (71).

In a phase I study of single agent olaparib, an oral PARP inhibitor, performed in a population of patients with advanced solid tumors enriched for tumors occurring in patients with *BRCA* mutations, clinical benefit was observed in 64% of *BRCA* mutation carriers while no responses were seen in patients with sporadic cancers (52). An expansion cohort of 50 patients with *BRCA* mutation-associated ovarian cancer confirmed these promising results with clinical benefit observed in 46% of *BRCA* mutation carriers (9). Based on these results, phase II studies evaluating olaparib in advanced pre-treated *BRCA* mutation-associated breast and ovarian cancers were performed. In the ICEBERG1 study, Tutt reported impressive response rates of 41% and 22% in patients with heavily pre-treated *BRCA* mutation-associated metastatic breast cancer treated with 400 mg and 100 mg twice

daily doses of olaparib respectively. Olaparib was well tolerated, causing only mild gastrointestinal toxicity, mild myelopsuppression and fatigue (72).

Iniparib, an intravenous drug initially thought to be a PARP inhibitor but now characterized by uncertain mechanism of action, has been evaluated in combination with gemcitabine and carboplatin in the treatment of a group of women with triple negative metastatic breast cancer, not specifically enriched for *BRCA* mutation carriers. In a randomized phase II trial, greater clinical benefit, improved progression-free survival and improved overall survival were observed with iniparib plus chemotherapy in comparison to chemotherapy alone (73). Unfortunately, results of a randomized phase III trial comparing iniparib plus chemotherapy to chemotherapy alone in triple negative metastatic breast cancer are disappointing with no demonstration of survival benefit (74). To date, iniparib has not been specifically evaluated in *BRCA* mutation-associated breast cancer.

Endocrine Therapy

As is the case with sporadic breast cancer, hormone receptor-positive *BRCA* mutation-associated breast cancer is treated with adjuvant endocrine therapy with the goals of reducing the risk of distant metastases and improving survival. Tamoxifen is used for pre-menopausal women and either aromatase inhibitors alone or tamoxifen followed by aromatase inhibitors are used for post-menopausal women (75).

As cited above, tamoxifen may reduce the risk of ipsilateral recurrence and future contralateral breast cancer in women with *BRCA* mutation-associated breast cancer (24, 26, 28, 30, 32, 34–36). However, there is some laboratory and clinical data to suggest that *BRCA1* mutation-associated breast cancer may be relatively resistant to tamoxifen. The protein product of the *BRCA1* gene interacts with estrogen receptor- α (ER- α), to which tamoxifen binds. Usually, tamoxifen suppresses cell proliferation and ER-α transcriptional activity; however, this suppression is blocked in *BRCA1*-deficient breast cancer cell lines, suggesting relative resistance to tamoxifen (51). Little clinical data exist addressing this issue but a small retrospective study comparing outcomes in early stage *BRCA* mutation-associated and sporadic breast cancer treated with endocrine therapy noted a lower overall survival observed in the *BRCA* carriers, suggesting relative resistance to adjuvant endocrine therapy with tamoxifen (76). These results, however, require confirmation and the use of adjuvant endocrine therapy is recommended in *BRCA* mutation-associated hormone receptor positive breast cancer. Unfortunately, there is no data yet regarding outcomes with aromatase inhibitors as adjuvant endocrine therapy in *BRCA* mutation-associated breast cancer.

Role of Oophorectomy in Management of *BRCA* Mutation-Associated Breast Cancer

A key difference between the management of sporadic and *BRCA* mutation- associated breast cancer is the role of oophorectomy. In premenopausal women with sporadic breast cancer, ovarian ablation, accomplished via either oophorectomy, ovarian irradiation or gonadotropin-releasing hormone analogs, is a therapeutic option which has been demonstrated to reduce the risk of breast cancer recurrence and mortality (77). In this setting, however, it remains controversial whether ovarian ablation improves outcomes achieved with tamoxifen alone and whether ovarian ablation should be combined with an aromatase inhibitor. Clinical trials addressing these issues are ongoing (78). For post-menopausal women with sporadic breast cancer, there is no role for ovarian ablation in improving breast cancer outcomes.

In contrast, due to their elevated risk of ovarian cancer, oophorectomy is recommended for women with *BRCA* mutation-associated breast cancer who are over age 35–40 and have completed childbearing regardless of menopausal status (19). The 10-year risk of ovarian cancer after breast cancer is 12.7% in *BRCA1* mutation carriers and 6.8% in *BRCA2* mutation carriers. In a prospective observational study of 491 women with early stage *BRCA* mutation-associated breast cancer, 25% of deaths occurring in women with stage I breast cancer were due to subsequent ovarian cancer, emphasizing the importance of preventing ovarian cancer in this population (3). Oophorectomy achieves three endpoints in *BRCA* mutation carriers: reduction in the risk of future ovarian cancer, reduction in the risk of future breast cancer, and, most importantly, reduction in mortality (38, 79, 80).

Oophorectomy has been estimated to reduce the risk of ovarian cancer in *BRCA* mutation carriers by at least 80–90%. This degree of risk reduction occurs regardless of menopausal status at the time of oophorectomy and has been observed in *BRCA* mutation carriers with and without a personal history of breast cancer (38).

With regard to preventing breast cancer, oophorectomy performed in premenopausal women with *BRCA* mutations has been estimated to reduce the risk by approximately 50%. However, when results of studies evaluating oophorectomy are stratified by personal history of breast cancer, the breast cancer prevention benefit of the procedure appears to be limited to unaffected women, with oophorectomy only preventing a first diagnosis of breast cancer in *BRCA* mutation carriers (38, 78, 79).

Due to the lower risk of ovarian cancer associated with *BRCA2* mutations when compared to *BRCA1* mutations and due to the fact that *BRCA1* mutation-associated breast cancer is more likely to be hormone receptor negative than *BRCA2* mutation-associated breast cancer, questions have arisen regarding whether the efficacy of oophorectomy in reducing the risk of ovarian and breast cancer is equivalent in *BRCA1* and *BRCA2* mutation carriers. In Domchek's multi-center, prospective cohort study of 2,482 women with *BRCA* mutations, bilateral salpingo-oophorectomy was associated with a statistically significant 69% reduction (HR 0.31, 95% CI 0.12–0.82) in the risk of ovarian cancer among *BRCA1* mutation carriers without a history of breast cancer and an 85% reduction (HR 0.15, 95% CI, 0.04–0.63) in the risk of ovarian cancer among *BRCA1* mutation carriers with a history of breast cancer. Among *BRCA2* mutation carriers with and without a history of breast cancer, no cases of ovarian cancer were observed after oophorectomy. With regard to breast cancer risk, oophorectomy was associated with a 37% reduction (HR 0.63, 95% CI, 0.41–0.96) in the risk of future breast cancer among *BRCA1* mutation carriers without prior breast cancer and a 64% reduction (HR 0.36, 95% CI, 0.16–0.82) in the risk of future breast cancer in *BRCA2* mutation carriers without a prior history of breast cancer. As stated above, there was no significant benefit of oophorectomy in preventing future breast cancer in mutation carriers with prior breast cancer (38). These findings support efficacy of oophorectomy in preventing breast and ovarian cancer in both *BRCA1* and *BRCA2* mutation carriers and the procedure is recommended for both groups.

Most importantly, Domchek found that oophorectomy is associated with significant mortality benefits in *BRCA* mutation carriers, including in those already diagnosed with breast cancer. In the latter group, bilateral salpingo-oophorectomy reduces all-cause mortality by 70% (HR 0.3, 95% CI, 0.17–0.52), and interestingly, despite a benefit in terms of breast cancer incidence, breast cancer-specific mortality was reduced by 65% (HR 0.35, 95% CI, 0.19–0.67). It is not known, however, whether the breast cancer-specific mortality benefit of oophorectomy in *BRCA* mutation carriers with a history of breast cancer is limited to women whose breast cancer is hormone receptor positive. Additionally, in carriers with

breast cancer, bilateral salpingo-oophorectomy is associated with a trend towards a 90% reduction in ovarian cancer-specific mortality (HR 0.1, 95% CI, 0.01–0.1.42) (38).

Among unaffected *BRCA* mutation carriers, bilateral salpingo-oophorectomy reduces all-cause mortality by 55% (HR 0.45, 95% CI, 0.21–0.95), breast cancer-specific mortality by 73% (HR 0.27, 95% CI, 0.05–1.33), and ovarian cancer-specific mortality by 61% (HR 0.39, 95% CI, 0.12–1.29) (38).

Conclusion

As described above, the management of *BRCA* mutation-associated breast cancer is complex and multiple factors regarding the cancer at hand and future cancer risks must be weighed together when making treatment decisions. With the availability of peri-diagnostic genetic testing, care plans which incorporate *BRCA* mutation status can now be developed. Women with *BRCA* mutation-associated breast cancer are candidates for either breast conserving therapy or mastectomy (usually performed with contralateral prophylactic mastectomy). Bilateral salpingo-oophorectomy in mutation carriers with breast cancer has been associated with significant decreases in ovarian cancer incidence, breast cancer-specific mortality and all-cause mortality. Thus, this procedure is recommended for women with *BRCA* mutation-associated breast cancer who have completed childbearing. At this time, decisions regarding systemic therapy are usually made without consideration of *BRCA* mutation status. However, promising data regarding cisplatin and PARP inhibitors in the treatment of *BRCA* mutation-associated breast cancer may soon change this paradigm. Despite these advances, personalized cancer medicine is in its infancy, and there remain many unanswered questions regarding the management of *BRCA* mutation-associated breast cancer. For example, it is not known whether the effects of cisplatin and PARP inhibitors are equivalent in *BRCA1* and *BRCA2* mutation-associated breast cancer and there is currently no data regarding outcomes with aromatase inhibitors in the management of *BRCA* mutation-associated breast cancer. With time, these and other questions will be answered and we will become better able to individually tailor treatment and prevention plans for women with *BRCA* mutation-associated breast cancer.

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Table

Clinical Factors Which Modulate the Risk of Future Ipsilateral and Contralateral Breast Cancer in *BRCA1/2* Mutation Carriers with Breast Cancer

Clinical Factor	**Effect on Risk of Future Ipsilateral Breast Cancer**	**Effect on Risk of Future Contralateral Breast Cancer**
Young Age at Diagnosis	↑	↑
Gene Mutated (*BRCA1* or *BRCA2*)	No Effect	*BRCA1* > *BRCA2*
Adjuvant Tamoxifen	↓ / No Effect *	↓ / No Effect *
Adjuvant Chemotherapy	↓	↓ / No Effect *
Oophorectomy	↓ / No Effect *	↓
Contralateral Prophylactic Mastectomy	No effect	↓
Radiation to the Affected Breast	↓	No effect

* Reduction in risk demonstrated in some studies, but not confirmed in all studies. Uncertain if this clinical factor independently modulates risk of future ipsilateral and/or contralateral breast cancer in *BRCA1/2* mutation carriers with breast cancer.