Management Strategies of Breast Cancer Patients with BRCA1 and BRCA2 Pathogenic Germline Variants

Sarah Edaily, Hikmat Abdel-Razeq

Abstract: Most of breast cancer cases are sporadic; however, 15–20% are associated with family history, and some are inherited. Among those, deleterious mutations in BRCA1 and BRCA2 tumor suppressor genes are the most commonly encountered pathogenic germline variants (PGVs). Given the availability and affordability of multi-gene panel sequencing technologies, testing for PGVs is commonly practiced. With our enhanced understanding of cancer genetics and specific molecular alterations, the better acceptance of risk-directed screening and prevention, and the recent introduction of novel targeted therapies, management of BRCA-positive breast cancers is taking a new direction, focusing more on risk-reducing interventions, including mastectomy and salpingo-oophorectomy, and incorporating special treatment regimens, including platinum-based chemotherapy, and the recently-introduced PARP (poly (ADP)-ribose polymerase) inhibitors. Given the recent advances in reproductive technology and molecular medicine, younger women with PGVs may have the option of embryo selection through preimplantation genetic testing and diagnosis, thus preventing the potential transmission of the implicated genes to the next generations. In this review, we cover the clinical implications of identifying a pathogenic germline mutation in BRCA1 and BRCA2 genes in breast cancer patients, and their relatives, across the continuum of care – from cancer prevention and early detection, through active treatment and up to survivorship issues.

Keywords: breast cancer, BRCA1, BRCA2, germline mutation, risk-reducing surgery

Introduction

Breast cancer continues to be the most commonly diagnosed cancer among women worldwide. Though more than 80% of breast cancers are sporadic, 15–20% of such tumors are associated with family history of breast or other cancers, and some are inherited. Deleterious mutations in BRCA1 and BRCA2 tumor suppressor genes are the most common causes of hereditary breast and ovarian cancer syndrome. The respective protein products of each gene function as a gatekeeper involved in the repair of DNA double strand breaks by homologous recombination and ensure the faithful replication of the genetic material with each cell division. Cells that lack this highly sophisticated protective mechanism, due to germline mutation in one of these in genes, will be prone to more mutations leading to higher risk of developing certain malignancies, with the breast and ovaries being the most likely affected organs.

Both BRCA1 and BRCA2 pathogenic variants are associated with high penetrance rate. In a prospective study from the United Kingdom (UK) of around 2000 BRCA1/2 mutation carriers, the estimated cumulative risk, by age 70, for BRCA1 mutation carriers was 60% (95% CI, 44–75%) for breast cancer, 59% (95% CI, 43–76%) for ovarian cancer, and 83% (95% CI, 69–94%) for contralateral breast cancer. On the other hand, women carrying BRCA2 mutation had a risk of 55% (95% CI, 41–70%) for breast cancer, 16.5% (95% CI, 7.5–34%) for ovarian cancer, and 62% (95% CI, 44–79.5%) for contralateral breast cancer.

In a more recent prospective cohort study of around 6000 BRCA1 and 3800 BRCA2 female carriers, the cumulative breast cancer risk, up to age 80, was 72% (95% CI, 65–79%) among BRCA1 carriers and 69% (95% CI, 61–77%) among BRCA2 carriers. On the other hand, cumulative ovarian cancer risk was 44% (95% CI, 36–53%) and 17% (95% CI, 11–25%) among BRCA1 and BRCA2 carriers, respectively. Contralateral breast cancer risk, 20 years after index breast cancer diagnosis, was 40% (95% CI, 35–45%) for BRCA1 and 26% (95% CI, 20–33%) for BRCA2 carriers.
Thanks to the availability and affordability of multi-gene panel sequencing technologies, and the recently established therapeutic implications of positive genetic testing in many cancer sites, including breast, ovarian, pancreatic and prostate cancers, identification of *BRCA1/2* and other pathogenic germline variants (PGVs) has become more common.\(^8\)

Until recently, the management of breast cancer in patients carrying a germline mutation in *BRCA1* or *BRCA2* genes was similar to that of other patients without these mutations, and was defined by tumor subtype and stage, among other patient- and tumor-related factors. However, the better understanding of cancer genetics and specific molecular alterations, the potential for risk-directed screening and prevention, and the recent introduction of novel targeted therapies, at various stages of disease management, led to better personalized management strategies.

In this paper, we cover the specific clinical implications of these inherited cancer predisposition syndromes in regard to prophylactic risk-reducing surgeries, specific concerns in systemic treatment, impacts on reproductive factors and other cancer survivorship issues.

**Pathological Features of BRCA-Associated Breast Cancer**

Many studies have shown that breast cancer among patients with *BRCA1* or *BRCA2* pathogenic variants may carry special pathological features that may impact on the aggressiveness of anti-cancer therapy.\(^4,9\) In a study that reviewed pathological features of *BRCA1* and *BRCA2*-associated breast cancer among 5000 patients, tumors in *BRCA1* carriers were more of higher grade and of triple-negative (TN) subtype, whereas hormone receptor-positive tumors were detected more often among *BRCA2* carriers. Additionally, *BRCA2*-associated cancers were more likely to contain calcifications that can be easily detected by mammography.\(^10,11\) Another prospective study enrolled a cohort of 1143 young females; 131 (11%) were *BRCA1* or *BRCA2* mutation carriers. *BRCA1*-associated tumors were more likely to be triple-negative, while those associated with *BRCA2* were described as aggressive hormone receptor-positive tumors (luminal B-like).\(^12\) In another retrospective study, 391 *BRCA*-negative women were compared to 86 women who carried a pathogenic *BRCA* mutation. Triple-negative disease was diagnosed in 57.1% of the *BRCA1*-positive patients, in 23.3% of the *BRCA2*-positive patients, and in 13.8% of the *BRCA*-negative patients. Additionally, patients with *BRCA1* mutation had higher nuclear grade, while frequency of estrogen receptors (ER) expression was not significantly different between mutation carriers and noncarriers, and clinical stage at diagnosis was almost similar between carriers and noncarriers.\(^13\)

Variation in pathological features of patients with mutated *BRCA1* or *BRCA2* can be better appreciated in studies that addressed the utilization of 21-gene recurrence score (RS) assay in such patients. A review from Memorial Sloan Kettering Cancer Center of *BRCA* mutation carriers with hormone receptor-positive, node-negative breast cancer who had Oncotype-DX\(^®\) testing showed that median RS was higher in cases versus controls (24 vs 16; \(P\text{-value} < 0.0001\)), with 28% having high-risk disease, 56% intermediate-risk and only 16% having low-risk disease. Investigators concluded that germline *BRCA1/2*-mutated hormone receptor-positive tumors have intrinsically less favorable biology and most patients have benefited from chemotherapy.\(^14\) In a similar more recent study from MD Anderson Cancer Center (MDACC), investigators evaluated a cohort of 745 patients with early-stage ER-positive, HER2-negative invasive breast cancer who had both Oncotype-DX Breast Recurrence Score\(^®\) analysis and genetic testing for hereditary breast and ovarian cancer syndrome. A total of 33 (4.4%) had pathogenic *BRCA1/2* mutations (8 *BRCA1*, 25 *BRCA2*). Patients with *BRCA1/2* mutations were younger, had less progesterone receptor (PR) expression, higher nuclear grade, and higher Oncotype DX Breast Recurrence Scores\(^®\) (with median RS of 29, compared to 16 in patients without mutations, \(P\text{-value} < 0.0001\)). Despite more aggressive treatment (more adjuvant chemotherapy), disease recurrence developed in 18% of patients with *BRCA* mutations and 9% of patient without. However, multivariate analysis of recurrence-free survival (RFS) was not significant, hazard ratio (HR) 1.519 [95% confidence interval (CI), 0.64–3.58; \(P\text{-value} = 0.3401\)].\(^15\)

**Prognosis and Survival**

Questions regarding treatment outcomes and prognosis of patients with germline pathogenic variants in *BRCA1* or *BRCA2*, compared to the majority of the others with wild type (WT), are frequently asked by patients and their relatives. Published data are not consistent, and answers are, obviously, not easy.

In a meta-analysis of 16 trials with more than 10,000 breast cancer patients included, pathogenic *BRCA1/2* mutations \((n=1325\) patients, 13%) were not associated with worse OS (HR 1.06, 95% CI, 0.84–1.34, \(P\text{-value} = 0.61\)). Additionally, worse OS was observed with increased ER expression in *BRCA1* cohorts, but not in patients with *BRCA2*.\(^16\) Another
prospective study from the UK followed 2733 patient with breast cancer diagnosis at age 40 or younger, and pathogenic BRCA1/2 mutations were detected in 338 (12%) women. At a median follow-up of 8.2 years, no significant OS difference was detected between BRCA-mutated and WT young patients.\textsuperscript{17}

Differences in treatment outcomes between BRCA1 and BRCA2 was evaluated using data from the Danish Breast Cancer Group database which showed lower 10-year OS and DFS for BRCA1 breast cancer patients (n=141): 78% (95% CI, 69–85%) and 74% (95% CI, 64–81%), respectively, compared to 88% (95% CI, 78–94%) and 84% (95% CI, 74–91%) for BRCA2 patients (n=96).\textsuperscript{18}

In a Chinese cohort of 480 women, BRCA mutation carriers had more lymph node involvement at diagnosis (66.7% vs 42.6%; \(P=0.011\)), and significantly worse breast cancer specific outcomes with 5-year disease-free survival of 73.3% compared with 91.1% in non-carriers (\(P=0.013\)). Even after adjustment for other clinical prognostic factors, having BRCA mutation remained an independent factor for poor prognosis.\textsuperscript{19}

A meta-analysis of 60 studies evaluated the effect of germline BRCA1/2 mutations on prognosis of breast cancer patients, and found that BRCA1 mutation carriers had a shorter OS compared with sporadic cases (HR 1.30, 95% CI, 1.11–1.52) and worse breast cancer-specific survival in patients with stage I–III (HR 1.45, 95% CI, 1.01–2.07). Similarly, BRCA2 carriers had worse breast cancer-specific survival (HR 1.29, 95% CI, 1.03–1.62), but no difference in OS was detected. However, patients with triple-negative disease and BRCA1/2 mutations had better OS than sporadic cases (HR 0.49, 95% CI, 0.26–0.92).\textsuperscript{20} Another meta-analysis of 34 studies reached similar conclusions; BRCA mutations were associated with shorter OS (BRCA1: HR=1.69, 95% CI, 1.35–2.12, \(P<0.001\); BRCA2: HR=1.50, 95% CI, 1.03–2.19, \(P=0.034\)), but with nonsignificant difference in breast cancer specific survival (BRCA1: HR=1.14, 95% CI, 0.81–1.16, \(P=0.448\); BRCA2: HR=1.16, 95% CI, 0.82–1.66, \(P=0.401\)) or event-free survival (BRCA1: HR=1.10, 95% CI, 0.86–1.41, \(P=0.438\); BRCA2: HR=1.09; 95% CI, 0.81–1.47, \(P=0.558\)).\textsuperscript{21}

More recently, a small study reviewed retrospectively the efficacy of endocrine therapy plus CDK 4/6 inhibitors in patients with HR-positive/HER2-negative advanced breast cancer. A total of 217 patients were included; 15 (6.9%) carried germline BRCA1/2, ATM or CHEK2 pathogenic variants. The majority of the patients (n=164, 75.6%) received CDK4/6 plus endocrine therapy as a first line. Median progression-free survival (PFS) was significantly shorter in patients with germline pathogenic variants (10.2 months), compared with WT and untested patients (15.6 and 17.6 months, respectively), \(P=0.002\). Similarly, median OS was worse in patients with germline pathogenic variants compared to those without (\(P=0.006\)). In multivariate analysis, mutation status was an independent prognostic factor of both PFS (\(P=0.020\)) and OS (\(P=0.012\)).\textsuperscript{22}

**Risk-Reducing Surgery**

**Risk-Reducing Mastectomy**

Risk-reducing mastectomy provides maximum breast cancer risk reduction in BRCA mutation carriers in both retrospective and prospective data, with at least 90% risk reduction. Additionally, surgery has significant impact on quality of life by reducing the level of anxiety and fear of getting breast cancer.\textsuperscript{23} There are different surgical approaches for prophylactic mastectomy, but the gold standard is nipple-sparing, skin-sparing mastectomy with excellent oncological and esthetic results. The procedure is usually done through an inframammary, radial or axillary incision with skin carefully dissected off breast tissue with removal of the entire breast glands.\textsuperscript{23}

Mastectomy versus breast-conserving surgery (BCS) was not compared in randomized controlled trials. However, a systematic review of 18 studies published in 2019 compared BCS and mastectomy and showed almost comparable OS results from pooled analysis, with higher ipsilateral recurrence in the BCS group. Researchers concluded that BCS can be offered for select patients with BRCA mutation after proper counseling and with intensive follow-up.\textsuperscript{24} In another systematic review, 23 observational studies were analyzed to compare difference in outcomes between BCS and mastectomy in BRCA1/2 mutation carriers. A total of 3807 patients were included; 2200 (57.7%) had BRCA1 mutations while 1212 (31.8%) had BRCA2 mutations, and median age at diagnosis was 41 years. Mastectomy was performed on 1408 (41.5%) patients, while 2157 (56.7%) had BCS. Risk of locoregional recurrence was increased in the BCS group, but incidence of contralateral breast cancer, disease-free survival and disease-specific survival were not statistically different, and nor was the OS (HR: 1.10, 95% CI, 0.72–1.69, \(P=0.660\)) (Table 1).\textsuperscript{25} Data from the Danish Breast Cancer Group, however, showed that risk-reducing contralateral mastectomy results in a significantly reduced risk of death (adjusted OS HR 0.42, 95% CI, 0.21–0.84, \(P=0.01\)).\textsuperscript{18}
Risk-reduction decisions among cancer-free pathogenic BRCA1/2 mutation carriers from a single institution showed that 66% of 106 women went for surveillance only, while 34% opted for prophylactic mastectomy. Three factors were found to be significantly affecting women’s decision to have surgery: family member diagnosed with breast cancer below the age of 50 (OR: 4.67 [95% CI, 1.86–11.68], P=0.001), a relative died from cancer before age of 50 (OR: 2.26 [95% CI, 0.92–5.55], P=0.07) and having previous prophylactic oophorectomy (OR: 3.72 [95% CI, 1.49–9.31], P=0.005). Patients aged 30 or less were more likely to choose surveillance (OR: 0.2 [95% CI, 0.05–0.75], P=0.02).

In another study, prophylactic mastectomy was compared with therapeutic mastectomy in 30,803 patients from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database: 30,644 (99.5%) had therapeutic mastectomy, and only 159 (0.5%) had prophylactic mastectomy. Surgery duration was significantly longer in prophylactic mastectomy (265 vs 166 minutes; P<0.01), with no significant difference in mortality. After adjustment for age and surgery time, the prophylactic surgeries showed increase in thrombosis risk.

Risk-Reducing Salpingo-Oophorectomy (RRSO)

Risk-reducing salpingo-oophorectomy (RRSO) was addressed in the literature, highlighting two major points: first its effect on breast cancer recurrence and survival; and second, its obvious anticipated effect on reducing, or eliminating, ovarian cancer.

The impact of oophorectomy on survival of breast cancer patients with a BRCA1 or BRCA2 mutation was addressed in many studies. Many of these studies and registries have shown that RRSO provides significant reduction in breast cancer risk. In one retrospective study, 676 women with early-stage breast cancer and a BRCA1 or BRCA2 mutation were observed for up to 20 years after diagnosis. Bilateral risk-reducing oophorectomy was performed on 345 (51.0%) patients following their breast cancer diagnosis, while the others (n=331, 49.0%) opted to retain both ovaries. The 20-year survival for the entire cohort was 77.4%. The adjusted hazard ratio for death attributed to breast cancer in women who underwent oophorectomy was 0.57 (95% CI, 0.23–1.43; P=0.23) for BRCA2 carriers and 0.38 (95% CI, 0.19–0.77; P=0.007) for BRCA1 carriers. However, one prospective observational study reached different conclusions. In this study, 2272 BRCA1 and 1605 BRCA2 mutation carriers were followed for a mean of around 5 years, and 426 women developed breast cancer. Effect of RRSO were evaluated, and no significant benefit was noted in the BRCA1 cohort (HR=1.23; 95% CI, 0.94–1.61) or BRCA2 (HR=0.88; 95% CI, 0.62–1.24). However, BRCA2 mutation carriers had a potential benefit 5 years after RRSO.

Satisfaction of women following RRSO was much better than following prophylactic mastectomy. In a survey of 174 BRCA mutation carriers, 95% of them underwent prophylactic mastectomy and believed that this surgery can reduce breast cancer risk, but only 65% were completely satisfied from a cosmetic perspective. On the other hand, 90.5% of women who underwent RRSO would choose to do it again due to decreased anxiety about risk of ovarian cancer, though early menopausal symptoms had a significant impact on their quality of life and only 21% used treatments to relieve them.
Medical Treatment
Advanced-Stage Disease

The largest trial that addressed the benefit of platinum compound in the treatment of \textit{BRCA}-positive breast cancer was the TNT study which was a phase 3 randomized controlled trial conducted at 74 hospitals throughout the UK. The study compared carboplatin with docetaxel, a standard treatment for recurrent unresectable or metastatic triple-negative breast cancer. A total of 376 patients were randomized to receive carboplatin or docetaxel, both as single agent every three weeks until disease progression or intractable toxicity. The trial population largely comprised patients with TN breast cancer, and 43 (11.4%) had germline \textit{BRCA1} (\(n=31\)) or \textit{BRCA2} (\(n=12\)) mutation. Among the whole study group, there was no difference between the overall response rate (ORR) to carboplatin or to docetaxel (ORR, 31.4\% in the carboplatin group versus 34.0\% in the carboplatin group). Median PFS among patients allocated to carboplatin was 3.1 months (95\% CI, 2.4–4.2), and 4.4 months (95\% CI, 4.1–5.1) for those allocated to docetaxel, \(P=0.40\). Additionally, no difference was found in OS in both groups. On the other hand, patients with deleterious \textit{BRCA1}/2 germline mutation had a significantly better response to carboplatin than to docetaxel (ORR, 68\% versus 33.3\%, \(P=0.03\)). Results remained significant (\(P=0.01\)) after adjustment for known prognostic factors. Progression-free survival was also longer in subjects with a \textit{BRCA1}/2 germline mutation who were treated with carboplatin (median PFS, 6.8 months for carboplatin versus 4.4 months for docetaxel, \(P=0.002\)). However, no difference was found between groups in OS, which is obviously confounded by the crossover design of the study.\(^{32}\)

In another phase 2 nonrandomized trial, cisplatin was given to 20 \textit{BRCA1}-mutated patients with metastatic breast cancer. The overall response rate was 80\%, and OS at 3 years was 25\%.\(^{33}\) Response rate was also higher in a subgroup analysis from a multicenter phase 2 trial where cisplatin or carboplatin was given as first- or second-line treatment for patients with metastatic breast cancer; response rate was around 54\% in patients with pathogenic germline \textit{BRCA1}/2 mutations.\(^{34}\)

PARP (poly (ADP)-ribose polymerase) inhibitors were also tried in patients with mutated \textit{BRCA1}/2 advanced-stage breast cancer. The OlympiAD trial was a randomized phase 3 trial in which olaparib, at a dose of 300 mg twice daily, was compared to single agent palliative chemotherapy (capecitabine, eribuline or vinorelbine) in a cohort of 302 patients with pathogenic germline \textit{BRCA1}/2 mutation, HER2-negative metastatic breast cancer who received no more than two previous lines of chemotherapy in the metastatic setting. The study met its primary end point of PFS with a median PFS of 7 months versus 4.2 months (HR 0.58, 95\% CI, 0.43–0.80).\(^{35}\) However, there was no OS advantage even with an updated analysis of the study.\(^{36}\)

Talazoparib, another PARP inhibitor, was also studied in a phase 3 randomized trial, EMBRACA. In this open-label, randomized, phase 3 trial, 431 patients with HER2-negative locally advanced or metastatic breast cancer and deleterious or suspected deleterious germline \textit{BRCA1}/2 mutation were randomized to receive talazoparib at 1 mg orally once daily (\(n=287\)), or single agent chemotherapy (capecitabine, eribuline, gemcitabine or vinorelbine; \(n=144\)). Patients were allowed to be enrolled if they had received up to 3 previous cytotoxic regimens for advanced disease including a taxane, anthracycline or both. Treatment was continued until disease progression or unacceptable toxicity. Talazoparib showed statistically significant PFS benefit of 3 months (8.6 versus 5.6 months, HR 0.54, 95\% CI, 0.41–0.71).\(^{37}\) Similar to olaparib, talazoparib failed to show significant OS benefit in an updated analysis of the trial.\(^{38}\)

In a meta-analysis of the EMBRACA and the OlympiAD trials – the 2 major randomized controlled trials on PARP inhibitors used to treat advanced breast cancer – major hematologic adverse events, including anemia, neutropenia and decreased white cell count, were analyzed as a primary safety outcome, while fatigue and headache were considered as secondary safety outcome measures. Additionally, discontinuation rate and time to QoL deterioration were compared between the two PARP inhibitors. Olaparib caused less grade 3–4 anemia (OR=0.34, 95\% CI, 0.003–34.94) and less grade 3–4 neutropenia (OR=0.57, 95\% CI, 0.06–5.75) compared to talazoparib. In secondary safety analysis, olaparib was associated with higher grade 3–4 fatigue (OR=6.79, 95\% CI, 0.44–262.48) and less headache (OR=0.14, 95\% CI, 0.003–4.17). Time to clinically meaningful QoL deterioration was shorter with olaparib (HR=1.16, 95\% CI, 0.19–7.17) when compared to talazoparib. The authors concluded that both talazoparib and olaparib were well tolerated, with no
significant risk of discontinuation, and either agent can be used in the setting of metastatic or advanced HER2-negative breast cancer with *BRCA1/2* mutation with similar expected efficacy and safety.39

Another PARP inhibitor, veliparib, was evaluated in a randomized, double-blind, phase 3 trial (BROCADE3) in 509 patients with pathogenic germline *BRCA1/2* mutations and advanced HER2-negative breast cancer. A maximum of 2 prior lines of chemotherapy for advanced disease were allowed. Patients were randomized to carboplatin and paclitaxel combined with veliparib or with placebo until disease progression. Median PFS was 14.5 months (95% CI, 12.5–17.7) in the veliparib arm compared to 12.6 months (95% CI, 10.6–14.4) in the control arm (HR 0.71 [95% CI, 0.57–0.88], *P*=0.0016).40 In an exploratory analysis of the subset of patients who discontinued carboplatin and paclitaxel before disease progression and were continued on a higher dose of veliparib (300–400 mg twice daily continuously, *n*=136) or placebo (*n*=58), as maintenance, median PFS was 25.7 months with veliparib compared to 14.6 months with placebo. Adverse events in the maintenance phase were primarily gastrointestinal, while the most common grade 3 and 4 adverse events were neutropenia and anemia.41

Table 2 summarizes major studies that addressed treatment of advanced-stage breast cancer with pathogenic *BRCA1/2* variants.

### Early-Stage Disease

In the non-metastatic setting, platinum agents showed remarkable activity in *BRCA1/2*-mutated breast cancers. In an observational study in *BRCA1*-mutated patients with breast cancer, high rates of pCR were observed in a small group of patients who received neoadjuvant cisplatin (pCR in 10 of 12 patients, 83%), compared with 7% among those treated with cyclophosphamide, methotrexate and fluorouracil (CMF); 8% with doxorubicin and docetaxel; and 22% with doxorubicin and cyclophosphamide with and without fluorouracil.42 Another study confirmed pCR of 61% among 107 patients with pathogenic *BRCA1* mutation after neoadjuvant cisplatin chemotherapy.43 In a secondary analysis of GeparSixto randomized trial, 50 patients with pathogenic *BRCA1* or *BRCA2* germline mutations attained higher pCR.

#### Table 2 Treatment of Early-Stage Breast Cancer with Pathogenic BRCA1/2 Variants

<table>
<thead>
<tr>
<th>Treatment Phase</th>
<th>Study Name, Design</th>
<th>Author (Year) [Reference]</th>
<th>Inclusion</th>
<th>Number of Patients</th>
<th>Arms</th>
<th>Primary End Point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant</td>
<td>Retrospective review</td>
<td>Byrski et al (2010)12</td>
<td>Neoadjuvant with BRCA1 mutation in young patients (&lt;50 years)</td>
<td>102</td>
<td>Cisplatin or other chemotherapy</td>
<td>pCR</td>
<td>83% with cisplatin 7% with CMF 8% with AT 22% AC or FAC</td>
</tr>
<tr>
<td>Phase 2 trial</td>
<td>Byrski et al (2014)13</td>
<td>Stage I to III with BRCA1 mutation</td>
<td>107</td>
<td>Cisplatin 75 mg/m² every 3 weeks for 4 cycles</td>
<td>pCR</td>
<td>61% (65 of 107 patients)</td>
<td></td>
</tr>
<tr>
<td>GeparSixto, secondary analysis of RCT</td>
<td>Hahnen et al (2017)14</td>
<td>Previously untreated stage II–III, triple-negative</td>
<td>291 (50 with BRCA1 mutation)</td>
<td>Paclitaxel, doxorubicin, bevacizumab, Same plus carboplatin</td>
<td>pCR</td>
<td>65.4% versus 66.7% (no significant benefit)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>Olympia, Phase 3 RCT</td>
<td>Tutt et al (2021)15</td>
<td>HER2-negative early stage, pBRCA mutation and high clinicopathological riskb</td>
<td>1836</td>
<td>Olaparib versus Placebo for 1 year</td>
<td>3-year iDFS</td>
<td>85.9% vs 77.1% HR, 0.58; 95% CI, 0.41–0.82; <em>P</em>&lt;0.001.</td>
</tr>
</tbody>
</table>

**Notes:** aPegylated liposomal. bPatients with triple-negative breast cancer with >T1 or N+ or no pCR following neoadjuvant chemotherapy. Hormone-positive patients with pN2-3 or no pCR with a CPS+EG score of 3 or higher. The CPS+EG scoring system estimates relapse probability on the basis of clinical and pathological stage (CPS) and estrogen-receptor status and histologic grade (EG). Abbreviations: pCR, pathologic complete response; CMF, cyclophosphamide, fluorouracil, methotrexate; AT, doxorubicin and docetaxel; AC, doxorubicin, cyclophosphamide; FAC, fluorouracil, doxorubicin, cyclophosphamide; RCT, randomized controlled trial; iDFS, invasive disease-free survival; HR, hazard ratio; CI, confidence interval.
rate compared with patients without such mutations, but this rate was not increased by adding carboplatin to neoadjuvant chemotherapy.\textsuperscript{44}

PARP inhibitors were also tried in the setting of high-risk early-stage breast cancer with germline $BRCA1/2$ mutations and HER2-negative disease. Following the completion of standard local treatment and neoadjuvant or adjuvant therapy, 1836 patients were randomized to receive adjuvant olaparib for one year versus placebo in a randomized phase 3 trial (OlympiA). The 3-year invasive disease-free survival (iDFS) was significantly higher in the olaparib arm (85.9\% versus 77.1\%, $P<0.001$). Additionally, the 3-year distant disease-free survival (dDFS) was 87.5\% in the olaparib arm versus 80.4\% with placebo, $P<0.001$. Though the 3-year OS was better in the olaparib arm (92.0\% versus 88.3\%, $P=0.02$), it did not reach a prespecified $P$-value of less than 0.01.\textsuperscript{45} However, the results of the second preplanned event-driven analysis for OS were recently released. After a median follow-up of 3.5 years, there were 109 deaths in the placebo arm and 75 deaths in the olaparib arm; the 3-year OS rates were 89.1\% and 92.0\%, respectively (HR=0.68; 95\% CI=0.47–0.97, $P=0.0009$), crossing the pre-specified significance boundary.\textsuperscript{46}

Table 3 summarizes major studies that addressed treatment of early-stage breast cancer with pathogenic $BRCA1/2$ variants.

<table>
<thead>
<tr>
<th>Study Name, Design</th>
<th>Author (Year) [Reference]</th>
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<th>Number of Patients</th>
<th>Arms</th>
<th>Primary Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>Byrski et al (2012)\textsuperscript{33}</td>
<td>Metastatic with $BRCA1$ mutation</td>
<td>20</td>
<td>Cisplatin 75 mg/m$^2$ every 3 weeks, 6 cycles</td>
<td>ORR</td>
<td>ORR: 80% CR: 45% 3-year OS: 25%</td>
</tr>
<tr>
<td>TBCRC009, Phase 2</td>
<td>Isakoff et al (2015)\textsuperscript{14}</td>
<td>Metastatic TNBC; first- or second-line</td>
<td>11 (with $BRCA$ mutation)</td>
<td>Cisplatin or carboplatin</td>
<td>ORR</td>
<td>54.5% in $gBRCA$ mutation</td>
</tr>
<tr>
<td>TNT, Phase 3 RCT</td>
<td>Tutt et al (2018)\textsuperscript{12}</td>
<td>Advanced TNBC ($gBRCA$ and BRCAness subgroups)</td>
<td>43 (with $BRCA$ mutation)</td>
<td>- Carboplatin - docetaxel</td>
<td>ORR</td>
<td>68% versus 33%, $P=0.01$</td>
</tr>
<tr>
<td>OlympiAD, Phase 3 RCT</td>
<td>Robson et al (2017)\textsuperscript{15}</td>
<td>$gBRCA$ mutation, HER2–negative metastatic, after maximum of 2 chemotherapy lines</td>
<td>302</td>
<td>- Olaparib 300 mg BID versus - capcitabine, eribulin or vinorelbine</td>
<td>PFS</td>
<td>7.0 vs 4.2 months HR: 0.58; 95% CI: 0.43–0.80; $P=0.001$ OS not significant</td>
</tr>
<tr>
<td>EMBRACA, Phase 3 RCT</td>
<td>Litton et al (2018)\textsuperscript{17}</td>
<td>Noncurable locally advanced or metastatic HER2-negative, $gBRCA$ mutation, maximum of 3 prior regimens including taxane, anthracycline or both</td>
<td>431</td>
<td>- Talazoparib 1 mg daily - Capecitabine, eribulin, gemcitabine or vinorelbine</td>
<td>PFS</td>
<td>8.6 vs 5.6 months HR: 0.54; 95% CI: 0.41–0.71; $P=0.001$ OS not significant</td>
</tr>
<tr>
<td>BROCADE3, Phase 3 RCT</td>
<td>Diéras et al (2020)\textsuperscript{18}</td>
<td>Metastatic, HER2-negative $gBRCA$, up to 2 prior regimens</td>
<td>513</td>
<td>- Veliparib, carboplatin, paclitaxel - Carboplatin, paclitaxel</td>
<td>PFS</td>
<td>14.5 vs 12.6 months HR: 0.71 95% CI: 0.57–0.88 $P=0.0016$</td>
</tr>
</tbody>
</table>

**Abbreviations:** ORR, overall response rate; CR, complete response; OS, overall survival; TNBC, triple-negative breast cancer; RCT, randomized controlled trial; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.
Survivorship Issues

Bone Health

Women undergoing prophylactic oophorectomy while in their 40s are at higher risk for osteopenia and osteoporosis.\textsuperscript{47,48} Post-oophorectomy bone mineral density (BMD) measurements were assessed in a retrospective cohort of 95 women who had prophylactic oophorectomy at a mean age of 48 years. A significant annual decrease in BMD from baseline was noted among both pre- and postmenopausal women at time of surgery. Self-reported hormonal therapy use was significantly associated with less bone loss.\textsuperscript{49} Another retrospective study from Northern California reviewed bone health-related issues among 225 women who underwent RRSO due to pathogenic $BRCA1$ or $BRCA2$ mutations. The median time from RRSO to bone disease diagnosis was 29 months (range 1–170). After a median follow-up of 41 months from testing, 55.6\% had osteopenia, 12.1\% osteoporosis and 4\% had atraumatic fracture.\textsuperscript{50}

Recent evidence suggests that dysregulated RANK/RANKL system is a potential cause of breast cancer in women carrying $BRCA1$ mutations as these patients were found to have significantly lower levels of osteoprotegerin, which means less inhibition of RANKL-mediated signaling. As such, researchers are studying the potential role of denosumab in chemoprevention in such women.\textsuperscript{51–53} Besides regulating osteoclast differentiation and activation, the RANK/RANKL system has an important role in mammary gland physiology and in hormone-dependent epithelial cell proliferation during pregnancy. Hence, dysregulations in the RANKL/RANK system can play a role in breast cancer pathogenesis.\textsuperscript{54} Additionally, the role of dysregulated RANKL/RANK system is well established in the process of bone metastasis development. Such observations support the importance of RANKL inhibition in breast cancer prevention and therapy in both early and advanced-stage disease.

Some data also suggested an association between levels of expression of different RANK pathway molecules and breast cancer aggressiveness, development of bone metastasis and overall prognosis, though evidence is still conflicting and inconsistent.\textsuperscript{55–59}

Fertility and Reproduction

Healthy women and cancer patients who carry pathogenic $BRCA1/2$ mutations need special counseling for reproductive issues; several questions should be addressed in depth with both groups. The influence of pregnancy on the risk of breast or ovarian cancer is a concern for both healthy women and breast cancer patients with $BRCA1/2$ mutations. Though the issue is still controversial, one study suggested a differential association with parity between $BRCA1$ and $BRCA2$ mutation carriers.\textsuperscript{60,61}

Breastfeeding, on the other hand, can be protective. In a case-control study of more than 1500 pairs of women with $BRCA1$ or $BRCA2$ pathogenic mutations and matching patients with breast cancer and unaffected carriers of respective mutation as controls, investigators found significant reduction in breast cancer risk in $BRCA1$ carriers with reduction increased by increased duration of breast feeding: a 32\% reduction in risk for one year of breastfeeding (OR=0.68; 95\% CI, 0.52–0.91; \( P=0.008 \)). Breastfeeding for \( \geq 2 \) years conferred even a greater reduction in risk (OR=0.51; 95\% CI, 0.35–0.74). However, no significant difference was found among the $BRCA2$ cohort.\textsuperscript{62}

The optimal timing for risk-reducing bilateral mastectomies in healthy $BRCA1/2$ mutation carriers is more difficult to determine, as earlier removal of breast tissue before pregnancy can reduce the breast cancer risk; on the other hand, this will deprive the mother and her baby of the benefits of breastfeeding, so counseling of these young women should include personal preferences beside her expected risk based on mutation, age, breast density and family history.\textsuperscript{53} Additionally, data showed no difference in survival of patients carrying pathogenic BRCA mutations if they became pregnant after breast cancer diagnosis.\textsuperscript{64,65} Timing of contralateral risk-reducing mastectomy should take into consideration the expected patient prognosis from the first breast cancer. Another reason to advise women carrying pathogenic $BRCA1/2$ mutations to complete reproductive life as early as possible is the concern, although controversial, that these pathogenic mutations can decrease the ovarian reserve in healthy carriers.\textsuperscript{66}

Healthy women and cancer patients carrying pathogenic $BRCA1/2$ mutations can safely undergo fertility preservation by oocyte or embryo cryopreservation, but not ovarian tissue preservation, and data also showed that treatment of infertility, including IVF, can be safely implemented.\textsuperscript{63,67}
For women who choose to delay risk-reducing mastectomy an intensive surveillance approach should be carried out including annual mammography and breast MRI alternating every six months starting at age of 25–30 years or earlier based on the earliest age of cancer diagnosis in the family, and to avoid delays in diagnosis patients and physicians should be aware of the possibility of breast cancer occurrence during pregnancy and breastfeeding.68–70

Given the recent advances in molecular medicine and reproductive technology, BRCA-pathogenic variant carriers of reproductive age may have the option of Preimplantation Genetic Testing for Monogenic disorders (PGT-M). The Ethics Taskforce of the European Society of Human Reproduction and Embryology (ESHRE), in 2003, has considered PGT-M acceptable for hereditary breast and ovarian cancers,71 and, in 2008, Jasper et al reported the first live birth following PGT-M for a woman carrier of BRCA1 pathogenic variant.71,72 Since then, multiple studies have documented the success and the feasibility of PGT-M for women with BRCA pathogenic variants.73 Women’s attitude toward PGT-M is very variable and may be influenced by their age, family size and personal and family history of cancer.74–76 Cost of the procedure may also affect the uptake.

Lifestyle Modifications
Several studies have tried to investigate if harmful lifestyle factors such as obesity, smoking, alcohol and physical inactivity can influence cancer prevalence among BRCA1/2 mutation carriers. In the Lifestyle Intervention Study in Women with Hereditary Breast and Ovarian Cancer (LIBRE), researchers collected data from 68 BRCA1 and BRCA2 mutation carriers. At study entry, factors such as medical history, lifestyle behavior and socioeconomic status were retrospectively documented by interview, and the current BMI was recorded. The baseline measurements were compared within the cohort, and presented with reference values for the German population. Participants who had higher physical activity during their adolescence showed a significantly lower cancer prevalence (P=0.019). A significant difference in cancer occurrence was observed between smokers and non-smokers (P<0.001). Mutation carriers with no disease had a significantly higher physical activity level than diseased mutation carriers (P=0.046).77,78 Using a large international pooled cohort of BRCA1 and BRCA2 mutation carriers, another study confirmed the association between smoking of more than 5 years’ duration before a first full-term pregnancy (FFTP), but not alcohol consumption, and risk of breast cancer. The study included was conducted retrospectively (5707 BRCA1 mutation carriers and 3525 BRCA2 mutation carriers) and prospectively (2276 BRCA1 mutation carriers and 1610 BRCA2 mutation carriers).79

In a recent review, researchers reviewed data from 16 clinical trials trying to collect evidence regarding impact of lifestyle factors, or mainly metabolic effects, in women carrying pathogenic BRCA1/2 mutations on the risk of developing breast cancer. The authors concluded that smoking, obesity and sedentary life, especially in postmenopausal women, may be associated with increased risk, though the data are still controversial.80

Future Directions and Conclusions
Testing of patients with breast cancer for pathogenic germline variants, mostly BRCA1 and BRCA2, is widely available and has become more affordable. Implications of positive testing goes far beyond cancer prevention for patients and their relatives. Recent data have suggested that cancer patients, like those with breast, ovarian, pancreatic and prostate cancer who carry pathogenic variants, might be treated differently using many of the recently introduced drugs, in both early and advanced-stage disease. Clinical oncologists should widen the spectrum of cancer care offered to include extensive discussion of potential genetic and inherited etiology for the cancer they have.

Abbreviations
BCS, breast-conserving surgery; BMD, bone mineral density; CDK 4/6, cyclin-dependent kinase 4/6; DFS, disease-free survival; dDFS, distant disease-free survival; ER, estrogen receptor; FFTP, first full-term pregnancy; iDFS, invasive disease-free survival; IVF, in vitro fertilization; HR, hormone receptor; ORR, overall response rate; OS, overall survival; PARP, poly(ADP)ribose polymerase; PFS, progression-free survival; PR, progesterone receptor; PGV, pathogenic germ-line variants; pCR, pathologic complete response; QoL, quality of life; RANK, receptor activator of nuclear factor kappa-B; RANKL, receptor activator of nuclear factor kappa-B ligand; RRSo, risk-reducing salpingo-oophorectomy; RS, recurrence score; TN, triple-negative; WT, wild type.

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Author Contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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