



BRCA1/BRCA2 Pathogenic Variant Breast Cancer: Treatment and Prevention Strategies

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Hereditary breast cancer is known for its strong tendency of inheritance. Most hereditary breast cancers are related to *BRCA1/BRCA2* pathogenic variants. The lifelong risk of breast cancer in pathogenic *BRCA1* and *BRCA2* variant carriers is approximately 65% and 45%, respectively, whereas that of ovarian cancer is estimated to be 39% and 11%, respectively. Therefore, understanding these variants and clinical knowledge on their occurrence in breast cancers and carriers are important. *BRCA1* pathogenic variant breast cancer shows more aggressive clinicopathological features than the *BRCA2* pathogenic variant breast cancer. Compared with sporadic breast cancer, their prognosis is still debated. Treatments of *BRCA1/BRCA2* pathogenic variant breast cancer are similar to those for *BRCA*-negative breast cancer, mainly including surgery, radiotherapy, and chemotherapy. Recently, various clinical trials have investigated poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor treatment for advanced-stage *BRCA1/BRCA2* pathogenic variant breast cancer. Among the various PARP inhibitors, olaparib and talazoparib, which reached phase III clinical trials, showed improvement of median progression-free survival around three months. Preventive and surveillance strategies for *BRCA* pathogenic variant breast cancer to reduce cancer recurrence and improve treatment outcomes have recently received increasing attention. In this review, we provide an information on the clinical features of *BRCA1/BRCA2* pathogenic variant breast cancer and clinical recommendations for *BRCA* pathogenic variant carriers, with a focus on treatment and prevention strategies. With this knowledge, clinicians could manage the *BRCA1/BRCA2* pathogenic variant breast cancer patients more effectively.

Key Words: *BRCA1/BRCA2* pathogenic variant, Breast cancer, Ovarian cancer, Treatment, Prevention

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INTRODUCTION

Hereditary breast cancer accounts for 5–10% of all breast cancer cases [1]. Its genesis is associated with the pathogenic variant of certain genes; in more than 90% of cases, pathogenic variants are detected in *BRCA1* (MIM No. 113705)/*BRCA2* (MIM No. 600185) and are inherited in an autosomal dominant fashion [2]. By the age of 70 years, pathogenic variant of *BRCA1/BRCA2* augments the risk of breast cancer by 65% (44–78%)

and 45% (31–56%), respectively, and that of ovarian cancer by 39% (18–54%) and 11% (2.4–19%), respectively [3]. Furthermore, *BRCA* pathogenic variants are known to increase the risks of fallopian tube cancer, melanoma, endometrial cancer, pancreatic cancer, prostate cancer, and colorectal cancer [4-9] (Fig. 1).

BRCA stands for “BReast CAncer gene,” indicating its relevance in breast cancer pathogenesis. However, the gene itself does not induce breast cancer. Instead, *BRCA1/BRCA2* are in-

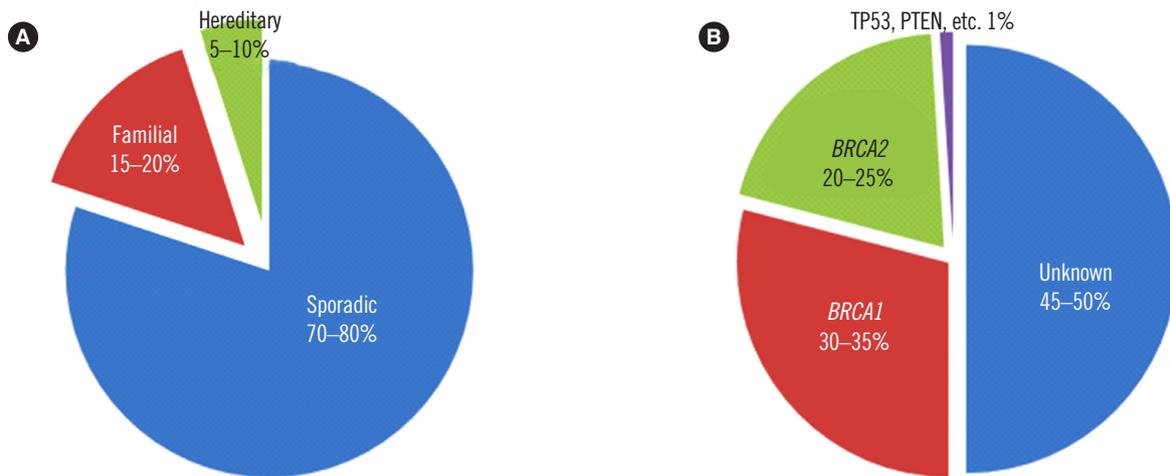


Fig. 1. Incidence of breast cancer. (A) hereditary breast cancer accounts for 5–10% of all breast cancer cases. (B) *BRCA1/BRCA2* pathogenic variant breast cancer accounts for up to 60% of all hereditary breast cancer cases [97]. Copyright permission for this figure was obtained from publisher.

involved in DNA repair of other genes that induce human cancers. *BRCA1* and *BRCA2* are two distinct cancer suppression genes and are essential in activating DNA repair in response to cellular stress [10-12]. *BRCA1/BRCA2* play crucial roles in chromatin remodeling, transcription control, cell-cycle regulation, and DNA-repair processes [13], and their tumor-suppressive effects have been attributed mainly to cell-cycle checkpoint and DNA repair management. Nevertheless, the detailed mechanisms of carcinogenesis induced by *BRCA1/BRCA2* germline pathogenic variants in breast and ovarian tissues are yet unrevealed [14, 15]. The *BRCA1* gene is located on chromosome 17q21 and has 22 exons. It encodes a 1,863-amino-acid-long nuclear protein. *BRCA1* is expressed in various tissues, including breast and ovarian tissues [16]. The *BRCA2* gene is located on chromosome 13q12-13 and has 27 exons [17-20]. *BRCA1* and *BRCA2* have similar exon structures but do not show sequence homology [21].

There are more than 1,600 and 1,800 known variants in *BRCA1* and *BRCA2*, respectively, the majority of which induce frame-shifts, leading to missense or non-functional proteins [22]. In addition to breast cancer, *BRCA1* pathogenic variants increase the risks of ovarian cancer in women and prostate cancer in men, whereas *BRCA2* pathogenic variants increase the risks of cholangiocarcinoma, gastric cancer, and melanoma [23, 24]. This review provides an overview of the clinical perspectives of *BRCA1/BRCA2* pathogenic variant breast cancer and clinical recommendations for *BRCA* pathogenic variant carriers, with a focus on treatment and prevention strategies.

Clinicopathological characteristics of *BRCA1/BRCA2* pathogenic variant breast cancer

Clinicopathological characteristics of *BRCA* pathogenic variant and sporadic breast cancers differ from each other, and those of *BRCA1*- and *BRCA2*-related breast cancers also present distinct features from each other. In view of histological types, approximately 75% of *BRCA1* pathogenic variant breast cancers are invasive ductal carcinomas, and 10% are atypical medullary cancers. In *BRCA2* pathogenic variant breast cancer, lobular or ductal with lobular types are more frequent (in up to 10% of cases) [25]. Based on estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2) status, breast cancers can be classified into luminal A (ER⁺ and/or PR⁺ and HER2⁻), luminal B (ER⁺ and/or PR⁺ and HER2⁺), HER2-positive (ER⁻, PR⁻, and HER2⁺), and triple-negative (ER⁻, PR⁻, and HER2⁻) subtypes [26]. Triple-negative breast cancer (TNBC) shows aggressive biological behavior [27, 28]. It occurs in 10–15% of sporadic breast cancers and 66–100% of *BRCA1* pathogenic variant breast cancers. In contrast, 14–35% of TNBC cases carry a *BRCA2* pathogenic variant, which is more similar to the proportion in sporadic breast cancer [29, 30]. Moreover, *BRCA1* pathogenic variant breast cancers tend to have higher histological grade than *BRCA2* pathogenic variant breast cancers. Ductal carcinoma *in situ* (DCIS) is rare in *BRCA1* pathogenic variant carriers, but rather common in *BRCA2* pathogenic variant carriers [25] (Table 1).

The prognosis of *BRCA1/BRCA2* pathogenic variant breast cancer is debated. Some studies have indicated that *BRCA* pathogenic variants are related to adverse prognosis [31-33], whereas

Table 1. Clinicopathological characteristics of *BRCA1/BRCA2* pathogenic variants

	<i>BRCA1</i> pathogenic variant	<i>BRCA2</i> pathogenic variant
Chromosome	17q21	13q12-13
Breast cancer		
Risk of cancer (by 70 years)	65% (44–78%)	45% (31–56%)
Histological type	Invasive ductal (~75%) Atypical medullary (~10%)	Invasive ductal (~75%) Atypical medullary (<10%) Lobular or ductal with lobular feature type (up to 10%)
Histological grade	Mostly high (Grade III)	Mostly medium (Grade II) or high (Grade III)
TNBC	66–100%	14–35%
DCIS	Rare	Common
Ovarian cancer		
Risk of cancer (by 70 years)	39% (18–54%)	11% (2.4–19%)

Abbreviations: TNBC, triple-negative breast cancer; DCIS, ductal carcinoma *in situ*.

the predominant view is that prognoses of *BRCA* pathogenic variant and sporadic breast cancer do not differ [34–36]. A recent prospective study that compared prognoses of 338 *BRCA* pathogenic variant breast cancer patients (N=201 for *BRCA1* variants and N=137 for *BRCA2* variants) with those of 2,395 sporadic breast cancer patients revealed no difference (at two years: 97.0% vs 96.6%; at five years: 83.8% vs 85.0%; at 10 years: 73.4% vs 70.1%; hazard ratio [HR] 0.96 [95% confidence interval [CI] 0.76–1.22]; $P=0.76$). In addition, the TNBC subgroup (N=588) of *BRCA* pathogenic variant patients demonstrated better 2-year survival (95% vs 91%; HR 0.59 [95% CI 0.35–0.99]; $P=0.047$), but no definitive difference in 5-year (81% vs 74%; HR 1.13 [0.70–1.84]; $P=0.62$) and 10-year survivals (72% vs 69%; HR 2.12 [0.82–5.49]; $P=0.12$) [35]. In a meta-analysis by Baretta, *et al.* [37], *BRCA1/BRCA2* pathogenic variant patients had more favorable overall survival than *BRCA*-negative breast cancer patients (HR 0.49, 95% CI 0.26–0.92).

Treatment of *BRCA1/BRCA2* pathogenic variant breast cancer

Surgery and radiotherapy

The main treatment strategies for breast cancer are surgery and systemic treatment. One of the main concerns in surgical treatment of *BRCA1/BRCA2* pathogenic variant breast cancer is whether the treatment outcome of breast-conserving surgery (BCS) combined with radiotherapy is equivalent to that of radical mastectomy. There has been only one study thus far that compared

the results according to the method of operation (BCS vs mastectomy) in *BRCA1/BRCA2* pathogenic variant breast cancer [38]. According to that study, no significant difference was observed between overall survival of two groups (15-year survival rate; BCS: 91.7% vs mastectomy: 92.8%, $P=0.85$), while BCS group showed higher ipsilateral local recurrence rate than that of mastectomy group (15-year cumulative estimated risk 23.5% vs 5.5%, $P<0.0001$).

Other studies have addressed this issue by comparing the outcome of BCS in *BRCA1/BRCA2* pathogenic variant breast cancer to that of sporadic breast cancer [39–42]. Kirova, *et al.* [40] retrospectively assessed the prognosis of breast cancer patients who had BCS, by matching 131 *BRCA1/BRCA2* pathogenic variant breast cancer patients with 261 sporadic breast cancer patients. The mean follow-up duration was 161 months, and there was no significant difference in overall survival between the two groups. A retrospective case-control study for the breast cancer patients who underwent BCS revealed that breast cancer-specific survival rate did not differ between *BRCA* pathogenic variant and sporadic breast cancer patients [41]. A recent meta-analysis of 526 *BRCA1/BRCA2* pathogenic variant and 2,320 sporadic breast cancer patients revealed no difference in overall survival between these two groups [42]. However, in this study, *BRCA1/BRCA2* pathogenic variant breast cancer patients showed higher ipsilateral breast cancer recurrence than sporadic breast cancer patients with a median follow-up of longer than six years (relative risk [RR] 1.51, 95% CI 1.15–1.98).

Radiation following BCS is omitted only in very exceptional cases. Given the role of *BRCA* in DNA repair, concerns about complications of radiation therapy in *BRCA* pathogenic variant breast cancer have been raised. However, a study by Pierce, *et al.* [41] revealed no difference in radiation complication rates between *BRCA* pathogenic variant and sporadic breast cancers.

Chemotherapy

On DNA damage by chemotherapy, *BRCA1/BRCA2* induce a DNA damage response for repair. Thus, *BRCA* pathogenic variant status is considered a decisive factor in predicting chemotherapy sensitivity [43–45]. For instance, compared with those without, cells with *BRCA1* pathogenic variant are more sensitive to platinum-based chemotherapeutic agents, which disrupt the DNA structure [46, 47]. On the other hand, *BRCA1* pathogenic variant cells are somewhat resistant to microtubule-inhibiting chemotherapies, such as taxanes, *in vitro* [48, 49]. These *in vitro* findings have been corroborated by data from *BRCA* pathogenic variant breast cancer patients who underwent single tax-

ane-based neoadjuvant or palliative chemotherapy [50, 51]. However, there is insufficient evidence to exclude taxanes from adjuvant chemotherapy regimens in *BRCA* pathogenic variant breast cancer patients. Arun, *et al.* [50] reported that patients with ER⁺ *BRCA* pathogenic variant breast cancer showed a better pathological complete response than sporadic breast cancer patients when treated with anthracycline- and taxane-based neoadjuvant chemotherapy compared with those who were treated with single anthracycline-based chemotherapy. Moreover, prognoses of breast cancer patients who received anthracycline- and taxane-based chemotherapy were similar, regardless of *BRCA* pathogenic variant status.

Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor treatment

The promising systemic treatment drug for *BRCA* pathogenic variant is a PARP inhibitor [52]. PARP is essential for repairing DNA single-strand breaks through base excision repair. Inhibition of PARP leads to the accumulation of DNA single-strand breaks and eventually, replication fork damage. In normal cells, breaks are repaired by error-free homologous recombination. When there are defects in the homologous recombination pathway due to *BRCA* functional failure, PARP inhibitors induce synthetic lethality by hindering base excision repair [53-55]. Olaparib, talazoparib, rucaparib, niraparib, and veliparib are five PARP inhibitors currently available. Olaparib, rucaparib, and niraparib are approved by the United States Food and Drug Administration (FDA) for ovarian cancer treatment. Olaparib also obtained FDA approval for treatment of HER2⁻ metastatic germline *BRCA* pathogenic variant breast cancer [52].

The majority of clinical trials on PARP inhibitors in *BRCA* pathogenic variant breast cancer patients are phase I or II trials, whereas olaparib and talazoparib have reached phase III trials [52, 56, 57]. A phase III trial of olaparib (OlympiAD trial) in metastatic breast cancer patients with HER2⁻/*BRCA* pathogenic variants involved 302 patients, 205 of whom were treated with olaparib and 97 with conventional chemotherapy. The olaparib group showed better median progression-free survival (7.0 vs 4.2 months; HR for disease progression or death, 0.58; 95% CI, 0.43–0.80; $P < 0.001$) [56]. A phase III trial of talazoparib (EMBRCA trial) in advanced breast cancer with *BRCA* pathogenic variant involved 431 patients, 287 of whom were administered talazoparib and 144 conventional chemotherapy. Talazoparib treatment resulted in more favorable median progression-free survival (8.6 vs 5.6 months; HR for disease progression or death, 0.54; 95% CI, 0.41–0.71; $P < 0.001$) [57]. Rucaparib is a selective PARP-1 and PARP-2

inhibitor [58]. In a phase II trial in metastatic breast and ovarian *BRCA* pathogenic variant cancer patients, 41% of patients who received intravenous rucaparib achieved stable disease status within three months, although the objective response rate (ORR) was only up to 2%. The ORR for oral rucaparib reportedly was 15% [59]. In a phase I trial of niraparib in advanced solid organ cancer patients, four patients had *BRCA* pathogenic variant breast cancer, and two of them achieved a partial response [60].

Recent PARP inhibitor studies have focused on combinations with platinum-based chemotherapies, such as cisplatin and carboplatin [61-66]. ER and/or PR is expressed in 21–22% of *BRCA1* pathogenic variant carriers and 65–77% in *BRCA2* pathogenic variant carriers. ER⁺ *BRCA1/BRCA2* pathogenic variant cancers tend to show more adverse clinical characteristics and higher histological grades than sporadic ER⁺ cancers [67-70]. Some clinical trials have applied olaparib or talazoparib in ER⁺ metastatic *BRCA1/BRCA2* pathogenic variant breast cancers and reported promising treatment outcomes [56, 71-73]; however, the number of participants was relatively small, and thus, further investigations in larger patient cohorts are needed.

Prevention of breast cancer in *BRCA1/BRCA2* pathogenic variant carriers

Prophylactic surgery

Additional considerations for surgery of pathogenic variant breast cancer are the roles of prophylactic contralateral mastectomy and salpingo-oophorectomy in patient prognosis. A study by Biglia, *et al.* [74] indicated that the probability of contralateral breast cancer 10 years after breast cancer surgery was 5% in sporadic breast cancer compared with 27% and 19% in *BRCA1* and *BRCA2* pathogenic variant breast cancer, respectively. However, contralateral mastectomy showed no survival gain in pathogenic variant carriers. According to these results, contralateral mastectomy in *BRCA1/BRCA2* pathogenic variant breast cancer should be carried out for preventing contralateral breast cancer, not for improving survival. Prophylactic bilateral salpingo-oophorectomy in *BRCA1/BRCA2* pathogenic variant breast cancer reduced ipsilateral and contralateral breast cancer recurrences [42]. Furthermore, it significantly decreased breast cancer mortality in *BRCA1/BRCA2* pathogenic variant breast cancer patients [75]. However, breast cancer mortality was reduced only in *BRCA1* pathogenic variant breast cancer patients [76]. Recent studies have indicated that *BRCA1/BRCA2* pathogenic variant carriers have a higher risk of ovarian cancer, which tends to occur at a younger age in *BRCA1* than in *BRCA2* pathogenic variant carriers [3, 77, 78]. Prophylactic salpingo-oophorectomy

in healthy *BRCA1/BRCA2* pathogenic variant carriers reportedly reduces the risk of ovarian cancer by more than 80% [79, 80]. Based on the above findings, prophylactic bilateral salpingo-oophorectomy should be considered in *BRCA1/BRCA2* pathogenic variant carriers not only to reduce the risk of breast cancer but also for protection against ovarian cancer.

Chemoprevention with tamoxifen

The primary preventive effect of tamoxifen (selective ER modulator) on breast cancer in *BRCA1/BRCA2* pathogenic variant carriers was examined by the National Surgical Adjuvant Breast and Bowel Project [81]. The breast cancer risk ratios in tamoxifen-treated *BRCA1/BRCA2* pathogenic variant carriers were 1.67 (95% CI, 0.32–10.70) and 0.38 (95% CI, 0.06–1.56), respectively. Based on these results, the protective effect of tamoxifen in *BRCA1/BRCA2* variant carriers is very limited, with a slightly better effect in *BRCA2* pathogenic variant carriers. This limited effect might be related to the limited number of cases in that study (i.e., eight and 11 *BRCA1* and *BRCA2* pathogenic variant carriers, respectively) [81]. Regarding the secondary preventive effect of tamoxifen, a study on 1,583 *BRCA1* and 881 *BRCA2* pathogenic variant carriers showed a 62% breast cancer risk reduction (95% CI, 0.27–0.55) in *BRCA1* pathogenic variant carriers and a 67% risk reduction (95% CI, 0.22–0.50) in *BRCA2* pathogenic variant carriers [82]. In that study, there were no differences in the risk reduction rate according to the hormone receptor status of the primary breast cancer. It has been suggested that aromatase inhibitors (AIs) can prevent breast cancer in postmenopausal women [83]; however, the preventive role of AIs in *BRCA1/BRCA2* pathogenic variant breast cancer has not been reported.

RECOMMENDATION OF BRCA PATHOGENIC VARIANT SCREENING IN BREAST CANCER PATIENTS

If a *BRCA1/BRCA2* pathogenic variant is suspected, genetic testing is required. The American Society of Clinical Oncology and National Comprehensive Cancer Network (NCCN) recommend genetic testing if the *BRCA* pathogenic variant risk is high, with risk factors including family history of *BRCA* pathogenic variant, family history of breast or ovarian cancer, diagnosis of breast cancer or ovarian cancer, male breast cancer, onset of breast cancer at young age, and diagnosis of TNBC at age 60 years or younger [84, 85]. More detailed *BRCA* genetic testing criteria are as follows: there are more than three breast cancer

patients in the family other than the patient, regardless of the age at diagnosis; there are two breast cancer patients in the family and at least one was diagnosed at an age under 50 years; the patient has breast cancer and another family member is diagnosed as having squamous ovarian cancer; the patient has bilateral breast cancer; the patient is diagnosed as having breast cancer at an age under 45 years; and the patient is also diagnosed as having squamous ovarian cancer. The NCCN guidelines recommend *BRCA* genetic testing if a breast cancer patient has two or more family members with a history of pancreas cancer or has more than two third-degree relatives diagnosed as having prostate cancer (Gleason score ≥ 7) [85].

Recently, US Preventive Services Task Force updated its recommendation for genetic testing for *BRCA1* and *BRCA2* pathogenic variants. It suggests assessment for women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* pathogenic variants with an appropriate brief familial risk assessment tool [86].

SURVEILLANCE OF BRCA PATHOGENIC VARIANT CARRIERS

The most frequent cancers in *BRCA* pathogenic variant carriers are breast and ovarian cancers in women and prostate cancer in men [2, 3, 87]. Regular screening for these cancers is recommended. Breast cancer screening in women should start at the age of 18 years with monthly self-examination, followed by regular breast examination by a physician from the age of 25 years. Annual breast magnetic resonance imaging is recommended for women of 25–29 years of age, and mammography should be added from the age of 30 years. Ovarian cancer screening by vaginal sonography and CA125 blood testing is suggested from the age of 30 years, despite the lack of evidence of its superiority over prophylactic salpingo-oophorectomy [88–91]. For men, monthly self-examination and annual breast examination by a physician should be started at the age of 35 years. Men are recommended to start prostate cancer screening at the age of 45 years [87, 92, 93]. *BRCA* pathogenic variants also increase colorectal and pancreatic cancer risks [93–96]; screening tests for these cancers should be performed according to general cancer examination principles [92].

CONCLUSIONS

We described clinical aspects of *BRCA1/BRCA2* pathogenic variant breast cancers. In *BRCA1/BRCA2* pathogenic variant

breast cancer patients, surgical and radiation treatment outcomes were not inferior to those in sporadic breast cancer patients. For systemic treatment, platinum-based chemotherapy is thought to be effective. PARP inhibitors have been introduced recently and are increasingly used in metastatic breast cancer patients with *BRCA1/BRCA2* pathogenic variants. To inhibit secondary breast cancer in *BRCA1/BRCA2* pathogenic variants patients, prophylactic contralateral mastectomy and salpingo-oophorectomy could be considered. Chemoprevention using tamoxifen has shown effectiveness in secondary breast cancer. However, its role in prevention of primary breast cancer in healthy *BRCA1/BRCA2* pathogenic variants carriers is not confirmed. If *BRCA1/BRCA2* pathogenic variants are suspected, *BRCA* genetic testing is required, and for carriers of these variants, genetic counseling is indispensable. Additionally, for the better treatment and genetic counselling of *BRCA1/BRCA2* pathogenic variants carriers, further studies on *BRCA* variants of uncertain significance, which account for 10–20% of *BRCA* genetic testing results, should be performed.

Author Contributions

Conceptualization and writing: Anbok Lee. Formal analysis: Byung-In Moon. Data curation: Tae Hyun Kim.

Conflicts of Interest

The authors have declared that there are no competing interests.

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