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

Anbok Lee, M.D., Ph.D.¹, Byung-In Moon, M.D., Ph.D.², and Tae Hyun Kim, M.D., Ph.D.¹

¹Department of Surgery, Busan Paik Hospital, Inje University College of Medicine, Busan, Korea; ²Department of Surgery, Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Korea

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

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-
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/BRA2* 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/BRA2* 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/BRA2* pathogenic variant breast cancer and clinical recommendations for *BRCA* pathogenic variant carriers, with a focus on treatment and prevention strategies.

**Clinicopathological characteristics of *BRCA1/BRA2* 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/BRA2* pathogenic variant breast cancer is debated. Some studies have indicated that *BRCA* pathogenic variants are related to adverse prognosis [31-33], whereas...
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 survival (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).

Table 1. Clinicopathological characteristics of BRCA1/BRCA2 pathogenic variants

|                        | BRCA1 pathogenic variant | BRCA2 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%)   | 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 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 variant 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 (EMBRACA 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
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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.

ORCID

Anbok Lee https://orcid.org/0000-0003-0860-3239
Byung-In Moon https://orcid.org/0000-0002-7441-8472
Tae Hyun Kim https://orcid.org/0000-0002-6675-8872

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