

# Prevalence of germline *BRCA1/2* pathogenic variants in unselected Korean patients with HER2-negative metastatic breast cancer: a nationwide prospective study (KCSG BR19-10)



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## Summary

**Background** Assessment of germline (g) *BRCA1/2* status is recommended for all patients with HER2-negative metastatic breast cancer (MBC) to identify candidates for poly(ADP-ribose) polymerase (PARP) inhibitor therapy, which is not always possible in clinical practice due to limited testing resources. In this study, we investigate the cross-sectional prevalence of g*BRCA1/2* pathogenic variant (PV) carriers in unselected Korean patients with HER2-negative MBC.

**Methods** Patients diagnosed with HER2-negative metastatic BC receiving palliative systemic treatment were eligible for inclusion in the study. Peripheral blood was prospectively drawn from each patient and g*BRCA1/2* status was assessed by next-generation sequencing using an NGeneBio BRCAacccuTest.

**Findings** A total of 586 patients were enrolled between October 2019 and March 2022, and the prevalence of g*BRCA1/2* PV was analyzed in 570 patients. The median age at enrollment was 54 years (interquartile range, 48–61) and 567 patients were female. Among the 570 patients with g*BRCA1/2* analysis, 481 had hormone receptor–positive/HER2-negative breast cancer (BC) and 89 had triple-negative breast cancer (TNBC). The overall prevalence of

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Translation: For the Korean translation of the abstract see the [Supplementary materials](#) section.

*gBRCA1/2* PV carriers was 7.4% (42/570, 95% confidence interval (CI) 5.4%–9.8%) in unselected patients with HER2-negative MBC [*gBRCA1*, 1.8% (95% CI 0.8%–3.2%), 10/570; *gBRCA2*, 5.6% (95% CI 3.2%–7.8%), 32/570]. The overall prevalence of *gBRCA1/2* PV carriers in Korean patients with HER2-negative MBC and a low risk of hereditary breast ovarian cancer syndrome (HBOC) was 5.7% [19/332, 95% confidence interval 3.5%–8.8%; TNBC 10.5% (95% CI 1.3%–33.1%), 2/19; *HR-positive/HER2-negative* 5.4% (95% CI 3.2%–8.6%), 17/313].

**Interpretation** Our study measured the size of the current underestimation of *gBRCA1/2* PV carriers in unselected Korean patients with HER2-negative MBC, particularly in patients without high risk factors for HBOC. An active screening strategy for unselected HER2-negative MBC should be pursued to avoid missing potential candidates for systemic treatment with PARP inhibitors.

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**Keywords:** Breast cancer; *BRCA1*; *BRCA2*; Prevalence; Chemotherapy

#### Research in context

##### Evidence before this study

Two phase 3 trials, OlympiAD and EMBRACA, established poly(ADP-ribose) polymerase (PARP) inhibitors as a standard treatment option for patients with HER2-negative metastatic breast cancer (MBC) and germline *BRCA1/2* (*gBRCA1/2*) pathogenic variants (PVs). A *gBRCA1/2* assessment is therefore recommended for every patient with HER2-negative MBC; however the supporting evidence on the prevalence of *gBRCA1/2* PV carriers in an unselected Korean population with this indication is lacking.

The prevalence of the *gBRCA1/2* carrier was 15.7% in the Korean Hereditary Breast Cancer study and 14.5% among unselected Korean patients ≤60 years of age with stage I–III triple-negative breast cancer (TNBC). In a subgroup analysis of the BREAKOUT prospective cohort study, the overall prevalence of the carrier was 6.7% among 45 Korean patients with HER2-negative MBC receiving first-line chemotherapy.

##### Added value of this study

This is the largest prospective study on the prevalence of *gBRCA1/2* PVs in unselected Korean patients with HER2-

negative MBC. In Korea, assessment of *gBRCA1/2* variant is reimbursed for patients with breast cancer who have risk factors for hereditary breast ovarian cancer syndrome (HBOC). In this study, the overall prevalence of *gBRCA1/2* PVs in Korean patients with HER2-negative MBC was 7.4% (42/570) overall and 5.7% (19/332) in patients without risk factors for HBOC. Forty-five percent (19/42) of diagnosed *gBRCA1/2* PV cases would not have been identified under the existing reimbursement criteria in Korea. The current reimbursement strategy therefore misses a diagnosis of *gBRCA1/2* PV carrier in a considerable number of patients with HER2-negative MBC.

##### Implications of all the available evidence

The present study supports current global guidelines that every patient with HER2-negative MBC should be tested for *gBRCA1/2* mutation, as approximately 5.7% (19/332) of patients with HER2-negative MBC without risk factors for HBOC are missing treatment opportunities with PARP inhibitors in current practice strategies in Korea.

#### Introduction

Breast cancer is the most common type of cancer and the leading cause of cancer-related deaths among women, both globally and in Korea.<sup>1</sup> The *BRCA1* and *BRCA2* genes regulate the homologous recombination-repair pathway, and dysfunctional mutations in these genes are associated with increased risks of breast, ovarian, prostate, and pancreatic cancer.<sup>2</sup>

Poly(ADP-ribose) polymerase (PARP) inhibition in *BRCA*-deficient tumor cells results in chromosomal instability and subsequent apoptosis. Two PARP inhibitors, olaparib and talazoparib, have shown significant progression-free survival (PFS) benefits in patients with HER2-negative MBC in phase 3 trials comparing

them with chemotherapy.<sup>3,4</sup> Global guidelines recommend that *gBRCA1/2* mutation status should be assessed as part of routine clinical practice in every patient with human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC).<sup>5–8</sup> However, in Korea *gBRCA1/2* testing is reimbursed only for patients at high risk of hereditary breast and ovarian cancer.

The prevalence of deleterious germline mutations in *BRCA1/2* among patients with breast cancer differs according to ethnicity, age, and medical or family histories.<sup>9</sup> Most of the available evidence regarding *gBRCA1/2* variants are from Caucasian populations, and data for Asian or Korean patients are lacking. In a

Chinese multicenter cohort of unselected breast cancer (BC), the overall prevalences of *gBRCA1/2* pathogenic variants (PVs) were 5.5% and 9.4%.<sup>10,11</sup> In a Korean study, the overall prevalence was 15.7% among 2403 patients with BC.<sup>12</sup> However, populations in these studies included patients with stage I–III BC irrespective of subtype and at high risk of carrying *gBRCA1/2* PVs, which does not align with the population that may potentially require PARP inhibitor treatment. In another Korean study, prevalence of *gBRCA1/2* PV was 13.1% in 999 patients with stage I–III triple negative breast cancer.<sup>13</sup> It is unknown how many populations with HER2-negative MBC and without high risk factors of *gBRCA1/2* PVs are potential candidates of PARP-inhibitor treatment. In the screening phase of the OlympiAD study, the prevalence of *gBRCA1/2* PV was 13.5% among Asian patients.<sup>14</sup> In the BREAKOUT study, one of the first to investigate the prevalence of *gBRCA1/2* in unselected patients with HER2-negative MBC starting first-line systemic chemotherapy, the prevalence was 9.0% in European patients and 10.6% in Asian patients.<sup>15</sup>

The aim of this study was to estimate the size of the patient population that comprises candidates for palliative PARP inhibitors among unselected Korean patients with HER2 MBC, including patients without high risk factors for *gBRCA* mutations and who are not indicated for *gBRCA* testing under the Korean medical insurance system.

## Methods

This observational, cross-sectional study included a prospective cohort component. Patients were prospectively enrolled from 22 institutions in Korea.

Eligible patients were those older than 19 years at the time of enrollment, who had received a diagnosis of unresectable or metastatic HER2-negative BC, and who are not amenable to curable aim of treatment. HER2 status was determined locally, using immunohistochemistry (IHC) and in situ hybridization according to the American Society of Clinical Oncology and College of American Pathologist guidelines on HER2 testing. Hormone receptor status was determined by IHC of estrogen receptors and/or progesterone receptors. Allred scores of  $\geq 3$  by IHC were defined as positive hormone receptor (HR) expression. When patients had undergone multiple tumor biopsies and the HR status was changed, the final subtype was determined in the following order: subtype at initial diagnosis of recurrent BC, at curative surgery, and biopsy before neoadjuvant chemotherapy. Patients were not selected based on clinical characteristics, presence of risk factors for *gBRCA1/2* pathogenic mutation, or number of prior lines of treatment, and those with previously known *gBRCA1/2* pathogenic mutation status were eligible. Each patient should have been regarded as a good

candidate for active palliative systemic treatment at time of enrollment, and those who with terminal cancer were deemed unsuitable for further systemic treatment due to any reason were excluded.

Peripheral blood was drawn prospectively, and *gBRCA1/2* mutational status were determined in a central laboratory by next-generation sequencing (NGS) using an NGeneBio *BRCA*accuTest (PLUS), irrespective of existing local germline *BRCA* mutation (*gBRCAm*) test results. All *gBRCA1/2m* variants were classified as pathogenic or likely pathogenic (deleterious *gBRCA1* and/or *gBRCA2* mutation; genetic variant suspected deleterious), benign or likely benign (wild-type; genetic variant favoring polymorphism; no mutation/deleterious mutation detected), or genetic variant of uncertain significance. All *gBRCA1/2* variants were classified for pathogenicity according to the American College of Medical Genetics and Genomics (ACMG) standards and guidelines. Clinical evidence for variant interpretation was sourced from ClinVar, ENIGMA, and the Korean Hereditary Breast Cancer (KOHBCA) study. The databases used for population frequency annotation were gnomAD (release 2.1.1), Korean Variant Archive (KOVA), Korean Reference Genome Database (KRGDB) (phase 2).

Archival tumor specimens available from either a primary or metastatic tumor were obtained from a subset of patients when possible to test for somatic *BRCA1/2* mutations, *PALB2*, homologous recombination deficiency (HRD) gene mutations, and other co-mutations based on *SOLID*accuTest HRD platform. The evaluated HRD genes included *ATR*, *BARD1*, *BLM*, *BRIP1*, *CHEK2*, *EMSY*, *ERCC1*, *FANCA*, *FANCD2*, *FANCF*, *FANCI*, *FANCM*, *MAD2L2*, *MRE11*, *NBN*, *RAD50*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RBBP8*, *SLFN11*, *TP53BP1*, *XRCC1*, *XRCC5*, and *XRCC6*.

Clinical data, including patient demographics and disease characteristics, medical history, treatment history, type of current and subsequent treatment, and treatment outcome including survival were retrospectively and prospectively collected from a review of medical records. Risk factors for *gBRCA1/2* PVs, including a history of bilateral BC, a family history of BC or ovarian cancer in first-or second-degree relatives, and age at first diagnosis of BC were also collected.

This study was approved by the institutional review board at Samsung Medical Center (approval number 2019-06-027-001), at each participating site (Appendix p.6) and the Korean Cancer Study Group (KCSG-BR19-10). Written informed consent was obtained from each patient prior to enrollment.

The primary objective was to assess the prevalence of *gBRCA* PVs in unselected Korean patients with HER2-negative MBC. Secondary objectives were the prevalence of each *gBRCA1* and *gBRCA2* PV according to tumor subtype (HER2-negative or TNBC) and other

clinical characteristics, treatment patterns by line of therapy at metastatic setting, clinical outcomes including distant metastases-free survival (DMFS) from the first diagnosis, PFS by line of therapy, and overall survival (OS) according to gBRCA pathogenic mutation status and tumor subtype.

We assumed that the annual number of patients with HER-negative unresectable/metastatic BC in Korea is approximately 20,000. To estimate the prevalence of gBRCA1/2 pathogenic mutations in this population with a 95% CI and 4% of margin error, a sample size of 537 patients was needed.

The full analysis set (FAS) comprised all enrolled, eligible patients who were tested for gBRCA1/2. The prevalence of gBRCA1/2 PVs was defined as the number of patients who had gBRCA1/2 pathogenic or likely pathogenic mutations divided by the size of the FAS. No gBRCA1/2 variants of unknown significance were included in the pathogenic variants. The prevalence of gBRCA1/2 PVs according to demographic and clinical characteristics was presented by descriptive statistics. The CI for proportions was calculated by binomial exact calculation.

We compared the DMFS, PFS, and OS according to the gBRCA1/2 PV status. DMFS was defined as the time from the date of first diagnosis of early breast cancer to the date of first diagnosis of distant recurrence. PFS was defined by the line of treatment estimated from the date of the first date of the treatment to the date of disease progression or death, whichever came first. OS was the time from the date of diagnosis of metastatic disease to the date of death from any cause. Survival was estimated by the Kaplan–Meier method and compared using a log-rank test; a significance level of <0.05 was used for the analysis. All statistical analyses were conducted using R software version 4.3.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

### Patient population

Between October 2019 and March 2022, a total of 586 Korean patients from 22 medical institutions were screened and provided consent for study enrollment. During screening, seven patients were excluded (3 due to a diagnosis of HER2-positive BC; 3 due to consent withdrawal; and 1 due to death) before undergoing any study procedures. The gBRCA1/2 mutational status was assessed in the remaining 579 patients; 9 were further excluded from the final analysis for not meeting pre-specified eligibility criteria (4 patients due to diagnosis of stage I–III BC; 3 patients due to a diagnosis of

HER2-positive BC; 2 patients due to a diagnosis of ovarian cancer). As a result, 570 patients with HER2-negative MBC were included in the FAS (Fig. 1). Patients' characteristics are presented in Table 1.

### Prevalence of gBRCA1/2 pathogenic variants

Of the 570 unselected patients with HER2-negative MBC, 42 (7.4%; 95% confidence interval [CI], 5.4%–9.8%) harbored a gBRCA1/2 PV (Fig. 2A). The BRCA1 PV was detected in 10 patients (1.8%; 95% CI, 0.8%–3.2%) and BRCA2 PV was detected in 32 (5.6%; 95% CI, 3.9%–7.5%) of 570 patients. No patients had both gBRCA1 and gBRCA2 PVs. Of the 332 patients without risk factors for HBOC, the prevalence of gBRCA1/2 PV was 5.7% (19/332, 95% CI 3.5%–8.8%).

The overall prevalence of gBRCA1/2 PVs in TNBC patients was 6.7% (6/89, 95% CI, 2.5%–14.1%). Among TNBC patients, the prevalence of a gBRCA1 pathogenic mutation was 3.4% (3/89, 95% CI, 7.0%–9.5%), and for gBRCA2 the prevalence was 3.4% (3/89, 95% CI, 7.0%–9.5%). In patients with TNBC and at high risk for gBRCA1/2 PVs as determined by the Korean Health Insurance Review and Assessment Service guidelines, which include an age younger than 60 years at first TNBC diagnosis, a family history of breast cancer, ovarian cancer, pancreatic cancer, or MBC within third-degree relatives, a history of bilateral breast cancer, ovarian cancer and/or pancreatic cancer, the prevalence of a gBRCA1/2 pathogenic mutation rate was 5.7% (4/70, 95% CI, 1.6%–14.0%) overall. For gBRCA1m, the rate was 4.3% (3/70, 95% CI 0%–12.0%) and for gBRCA2m 1.4% (1/70, 95% CI 0%–7.7%). In 19 patients with TNBC who do not have a high risk factor for gBRCA1/2 PVs and are not indicated for a gBRCA1/2 test under Korean insurance system, the prevalence of gBRCA1/2 PV variants was 10.5% (2/19, 95% CI, 1.3%–33.1%) overall; both patients had gBRCA2 PVs.

In 481 patients with HR-positive, HER2-negative MBC, the overall prevalence of gBRCA1/2 PVs was 7.5% (36/481, 95% CI, 5.3%–10.2%), for gBRCA1 it was 1.5% (7/481, 95% CI, 0.6%–3.0%) and for gBRCA2 6.0% (29/481, 95% CI, 4.1%–8.5%). In patients with high-risk features (males those, aged younger than 40 years at first diagnosis, a family history of BC, ovarian cancer, pancreatic cancer, or metastatic prostate cancer within third-degree relatives, or a history of BC, ovarian cancer and/or pancreatic cancer), the prevalence of gBRCA1/2 PVs was 11.3% (19/168, 95% CI, 7.0%–17.1%) overall; for gBRCA1 it was 3.0% (5/168, 95% CI, 1.0%–6.8%) and for gBRCA2 8.3% (14/168, 95% CI, 4.6%–13.6%). In 313 patients with HR-positive, HER2-negative subtypes who do not have high risk factors for gBRCA1/2 pathogenic variants and were not eligible for gBRCA1/2 test reimbursement by the Korean insurance system, the prevalence of gBRCA1/2 PVs was 5.4% (17/313, 95% CI, 3.2%–8.6%) overall; gBRCA1 0.6% (2/313) and gBRCA2 4.8% (15/313), respectively.

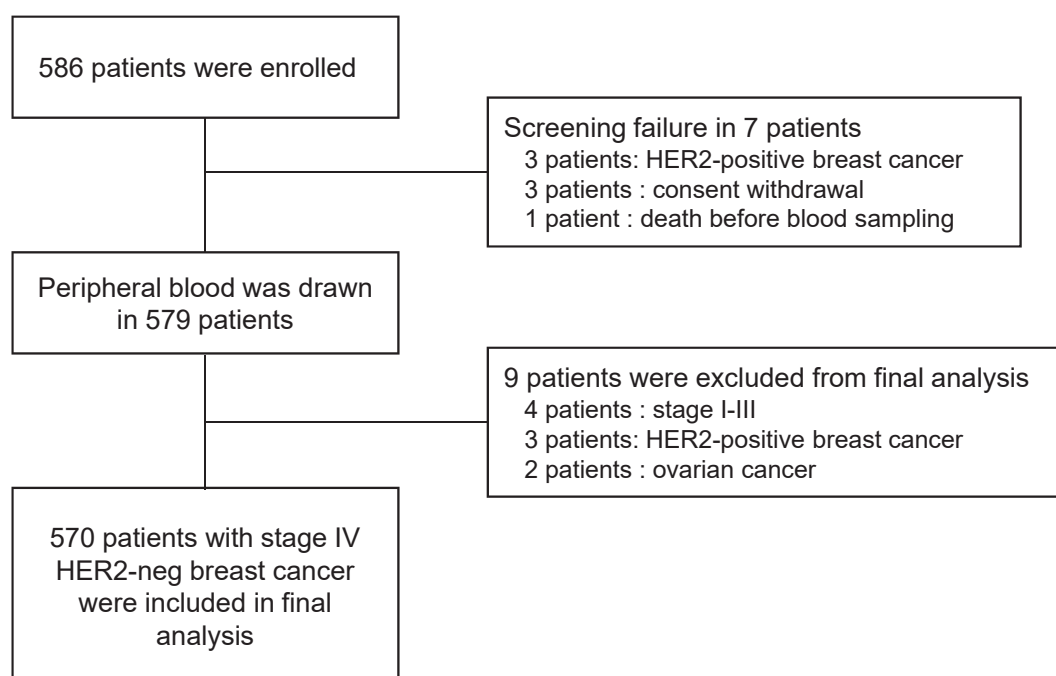


Fig. 1: Consort diagram.

The prevalence of *gBRCA1/2* PVs was higher when the patient was diagnosed with BC at a younger age. The overall prevalence was 12.8% (13/102; *gBRCA1*, 2.9%, 3/102 and *gBRCA2*, 9.8%, 10/102) in those diagnosed with BC at before 40 years of age, 7.5% (16/213; *gBRCA1*, 1.4%, 3/213 and *gBRCA2*, 6.1%, 13/213) in those in their 40s, 5.7% (10/174; *gBRCA1*, 2.3%, 4/174 and *gBRCA2*, 3.5%, 6/174) in those in their 50s, and 4.9% (4/81; all *gBRCA2*) in patients diagnosed with BC who were older than 60 (Fig. 2B).

The median age at first diagnosis of BC was 43 [interquartile range(IQR), 37–42] and 42 (IQR, 39–51) years in patients with *gBRCA1* and *gBRCA2* PVs, respectively, and younger than 48 (IQR, 42–55) years old in patients without *gBRCA1/2* PVs. The prevalence of premenopausal BC at first diagnosis, the presence of a family history of relevant cancer, and history of bilateral BC were higher in patients with *gBRCA1/2* PVs. The frequency of TNBC was higher in patients with *gBRCA1* PVs, and the patient group with *gBRCA2* PVs was enriched with HR-positive, HER2-negative subtypes. Baseline patients' characteristics are presented in Table 1.

#### Details of detected *gBRCA1/2* pathogenic variants

Among 10 detected *gBRCA1* PVs, four were single-nucleotide variations (SNVs) and four were frameshift indel mutations. Loss of copy number was suggested in four patients by NGS and two were finally confirmed. One patient had copy number loss in exon 1–13 and the other in exon 8–12. Variants of unknown significance

in *gBRCA1* were detected in 25 patients. Twenty-three types of *gBRCA2* PVs were detected in 32 patients; 21 were SNVs and 14 were frameshift indel mutations. Variants of unknown significance in *gBRCA1* were detected in 45 patients. Detailed mapping of *gBRCA1/2* PVs is presented in Table 2.

#### Assessment of somatic *gBRCA1/2* mutation

Archival tumor tissue for analysis of somatic mutation was obtained from 114 patients out of 570 patients in the FAS; 11 were excluded because of quality control failure. Among 103 patients who underwent NGS of a tumor, 8 with *gBRCA1/2* PVs had same somatic *BRCA1/2* mutations, among which somatic *BRCA2* c.1399A>T was classified as a tier 3 mutation. Two patients had a tier 1 somatic *BRCA1* mutation without a *gBRCA1/2* mutation. *PALB2* somatic mutations were detected in five patients; one was tier 2 and four were tier 3.

#### Clinical outcome according to *gBRCA1/2* pathogenic variants

With 71 (IQR 38–125) months of median follow-up of survival from first diagnosis, the median OS was 115.0 months (95% CI 95.5–134.5) in patients with HR-positive, HER2-negative subtype and 60. Months (95% CI 26.5–93.5) in patients with TNBC (Appendix p.2). OS was numerically longer in patients without a *gBRCA1/2* PV in patients with HR+/HER2– BC (median OS, 119 [95% CI 98.6–139.4 vs. 65 [95% CI 33.4–96.6] months,  $P = 0.083$ ) and in patients with TNBC (median OS, 60 [95% CI

|                                            | gBRCA1 PV N = 10 |      | gBRCA2 PV N = 32 |      | No gBRCA PV N = 528 |     |
|--------------------------------------------|------------------|------|------------------|------|---------------------|-----|
| Sex                                        |                  |      |                  |      |                     |     |
| Female                                     | 10               | 100% | 32               | 100% | 525                 | 99% |
| Male                                       | 0                | 0%   | 0                | 0%   | 3                   | 1%  |
| Age at first diagnosis of breast cancer    |                  |      |                  |      |                     |     |
| Median (IQR)                               | 43 (37–52)       |      | 42 (39–51)       |      | 48 (42–55)          |     |
| Age at enrollment                          |                  |      |                  |      |                     |     |
| Median (IQR)                               | 50 (41–60)       |      | 48 (41–56)       |      | 54 (49–62)          |     |
| Menopausal status at first diagnosis of BC |                  |      |                  |      |                     |     |
| Post                                       | 1                | 10%  | 6                | 19%  | 195                 | 37% |
| Pre                                        | 9                | 90%  | 24               | 75%  | 291                 | 55% |
| Unknown                                    | 0                | 0%   | 2                | 6%   | 39                  | 7%  |
| Family history of relevant cancer          |                  |      |                  |      |                     |     |
| Yes                                        | 4                | 40%  | 6                | 19%  | 43                  | 8%  |
| No                                         | 6                | 60%  | 25               | 78%  | 471                 | 89% |
| Unknown                                    | 0                |      | 1                | 3%   | 14                  | 3%  |
| Laterality of BC                           |                  |      |                  |      |                     |     |
| Bilateral                                  | 2                | 20%  | 3                | 9%   | 24                  | 5%  |
| Unilateral                                 | 8                | 80%  | 28               | 88%  | 503                 | 95% |
| Unknown                                    | 0                |      | 1                | 3%   | 1                   | 0%  |
| History of prior ovarian cancer            |                  |      |                  |      |                     |     |
| Yes                                        | 0                | 0%   | 0                | 0%   | 9                   | 2%  |
| No                                         | 10               | 100% | 32               | 100% | 514                 | 97% |
| Unknown                                    | 0                |      | 0                |      | 4                   |     |
| De novo stage IV                           |                  |      |                  |      |                     |     |
| De novo stage IV                           | 1                | 10%  | 14               | 44%  | 161                 | 30% |
| Recurrent                                  | 9                | 90%  | 18               | 56%  | 367                 | 70% |
| Subtype                                    |                  |      |                  |      |                     |     |
| HR+/HER2–                                  | 7                | 70%  | 29               | 91%  | 443                 | 84% |
| TNBC                                       | 3                | 30%  | 3                | 9%   | 83                  | 16% |
| Multiple primary                           | 0                |      | 0                |      | 2                   | 0%  |

**Table 1:** Patient characteristics by gBRCA1/2 pathogenic variants status.

23.4–96.6] months vs. 17 [95% CI 12.1–21.9] months,  $P = 0.11$ ) (Appendix p.3). Regarding DMFS, there was no statistical difference according to gBRCA1/2 PV (53.5 [95% CI 47.0–60.0] months vs. 49.6 [95% CI 15.3–83.9] months with gBRCA1/2 PV in HR+/HER2– BC,  $P = 0.16$ ; 20.2 [95% CI 17.0–23.4] months vs. 16.0 [95% CI 11.7–20.3] months with gBRCA1/2 PV in TNBC,  $P = 0.33$ ) (Appendix p.4).

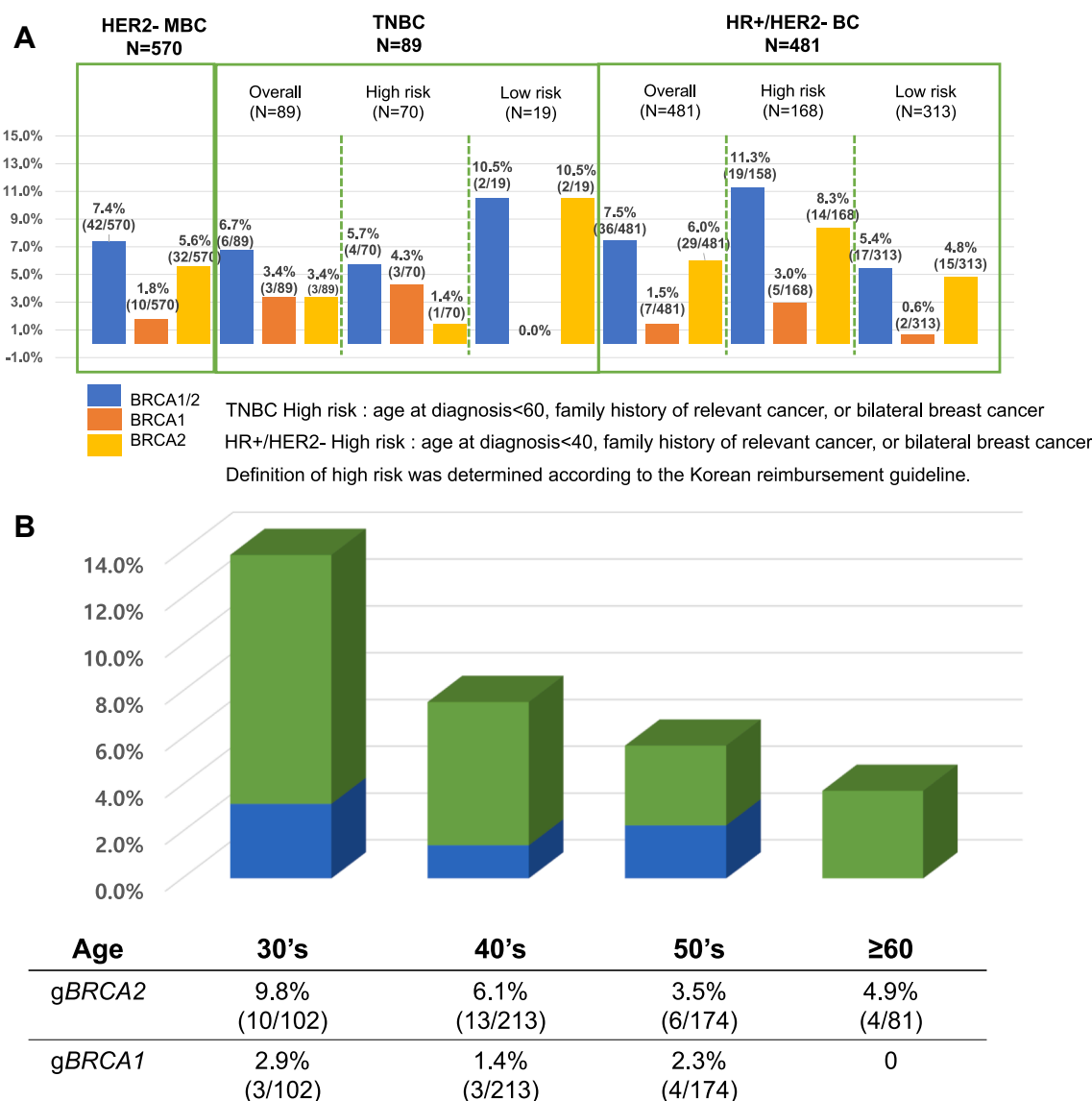
Among 443 patients with HR-positive, HER2-negative BC, 80% ( $n = 280$ ) received CDK4/6 inhibitors plus endocrine treatment in the first line; the median PFS in patients with gBRCA1 PVs was significantly shorter (2.6 [95% CI 1.7–3.6] months) than in those with gBRCA2 PVs (24.6 [95% CI 17.8–31.4] months) or without a gBRCA1/2 PVs (median PFS, 22.5 [95% CI 21.0–28.1] months,  $P < 0.0001$ ) (Appendix p.5). Median follow-up duration from the diagnosis of MBC was 35 (IQR 21–59) months.

## Discussion

In the present study, the overall prevalence of gBRCA1/2 PVs in an unselected Korean patients with HER2-

negative MBC was 7.4% (42/570, 95% CI, 5.4%–9.8%), which is within the reported range of 1.2%–9.7% in previous studies of gBRCA1/2 PVs in unselected HER2-negative MBC.<sup>16–22</sup>

In Korea, as of September 2024, gBRCA1/2 tests for female patients with BC are approved and reimbursed only for those with a family history of relevant cancer within third-degree relatives, diagnosis of BC at younger than 60 years old (in the case of TNBC) or than 40 years old (in other subtypes), bilateral BC, or a history of ovarian cancer or pancreatic cancer, while the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network recommend a gBRCA1/2 test for every patient with HER2-negative MBC regardless of risk factors for HBOC. In our study, the prevalence of gBRCA1/2 PVs among patients with HER2-negative MBC without these risk factors was 10.5% (2/19) in TNBC patients and 5.4% (17/313) in those with HR-positive, HER2-negative BC. In the BREAKOUT study, the gBRCA1/2m prevalence was 5.8% in patients without any risk factors.<sup>22</sup> Considering the current Korean reimbursement guidelines and the results of this study, the prevalence of gBRCA1/2 PVs



**Fig. 2:** Prevalence of gBRCA1/2 pathogenic variants in unselected Korean patients with HER2-negative metastatic breast cancer. **A.** Overall prevalence and prevalence by subtype and high risk factors (blue, gBRCA1/2 PV; orange, gBRCA1; yellow, gBRCA2; the definition of high risk was determined according to the Korean reimbursement guideline; TNBC high risk was defined as age at diagnosis <60 years, family history of relevant cancer, or bilateral breast cancer; HR+/HER2- high risk was defined as age at diagnosis <40 years, family history of relevant cancer, or bilateral breast cancer). **B.** Prevalence by age at initial diagnosis of breast cancer (blue, gBRCA1 PV; green, gBRCA2 PV).

in patients with HER2-negative MBC is likely being underestimated, both in TNBC and in HR-positive, HER2-negative subtypes. Assessment of gBRCA1/2 status is increasingly important, especially for those with HER2-negative BC, as they are candidates for PARP-inhibitor treatment, genetic counseling, and surveillance. Olaparib and talazoparib have shown statistically improved PFS compared with physician's choice treatment for HER2-negative MBC in a phase 3 trial, respectively.<sup>3,4</sup> In Korea, a gBRCA1/2 test by

Sanger sequencing is reimbursed and approved only for BC patients with high-risk features for gBRCA1/2 PVs, which is contrary to global guideline's recommendations that gBRCA mutation status should be assessed in every case of HER2-negative MBC, to identify candidates for PARP-inhibitor therapy. In this study we identified a subset of patients without high risk factors who have gBRCA1/2 PVs and who are prone to being neglected in clinics despite the possible potential benefit from PARP inhibitors. Expansion of

|       | Exon/<br>intron | HGVS nomenclature-<br>cDNA level | HGVS nomenclature-<br>Protein Change | Effect                 | Number |
|-------|-----------------|----------------------------------|--------------------------------------|------------------------|--------|
| BRCA1 | 6               | c.390C>A                         | p.Tyr130Ter                          | stop_gained            | 1      |
|       | 10              | c.3020del                        | p.Ser1007Ter                         | frameshift             | 1      |
|       | 10              | c.2048del                        | p.Lys683SerfsTer18                   | frameshift             | 1      |
|       | 10              | c.3627dup                        | p.Glu1210ArgfsTer9                   | frameshift             | 1      |
|       | 14              | c.4676-2A>C                      | –                                    | splice_acceptor&intron | 1      |
|       | 16              | c.5030_5033del                   | p.Thr1677IlefsTer2                   | frameshift             | 1      |
|       | 17              | c.5080G>T                        | p.Glu1694Ter                         | stop_gained            | 1      |
|       | 21              | c.5339T>C                        | p.Leu1780Pro                         | missense               | 1      |
|       | Exon/<br>intron | HGVS nomenclature-<br>cDNA level | HGVS nomenclature-<br>Protein Change | Effect                 | Number |
| BRCA2 | 2               | c.3G>A                           |                                      | Start lost             | 1      |
|       | 5               | c.475+1G>T                       |                                      | Splice_donor&intron    | 1      |
|       | 10              | c.1888dup                        | p.Thr630AsnfsTer6                    | frameshift             | 1      |
|       | 10              | c.1399A>T                        | p.Lys467Ter                          | stop_gained            | 4      |
|       | 10              | c.1796_1800del                   | p.Ser599Ter                          | Frameshift             | 1      |
|       | 11              | c.3744_3747del                   | p.Ser1248ArgfsTer10                  | Frameshift             | 1      |
|       | 11              | c.4829_4830del                   | p.Val1610GlyfsTer4                   | Frameshift             | 1      |
|       | 11              | c.2798_2799del                   | p.Thr933ArgfsTer2                    | Frameshift             | 2      |
|       | 11              | c.2983G>T                        | p.Gly995Ter                          | stop_gained            | 1      |
|       | 11              | c.3195_3198del                   | p.Asn1066LeufsTer10                  | Frameshift             | 1      |
|       | 11              | c.2912T>G                        | p.Leu971Ter                          | stop_gained            | 1      |
|       | 11              | c.5576_5579del                   | p.Ile1859LysfsTer3                   | Frameshift             | 1      |
|       | 11              | c.3744_3747del                   | p.Ser1248ArgfsTer10                  | Frameshift             | 1      |
|       | 11              | c.5576_5579del                   | p.Ile1859LysfsTer3                   | Frameshift             | 1      |
|       | 11              | c.4471_4474del                   | p.Leu1491LysfsTer12                  | Frameshift             | 1      |
|       | 11              | c.5344C>T                        | p.Gln1782Ter                         | frameshift             | 1      |
|       | 13              | c.6952C>T                        | p.Arg2318Ter                         | stop_gained            | 2      |
|       | 15              | c.7480C>T                        | p.Arg2494Ter                         | stop_gained            | 4      |
|       | 18              | c.8009C>T                        | p.Ser2670Leu                         | missense               | 1      |
|       | 20              | c.8572del                        | p.Gln2858AsnfsTer5                   | frameshift             | 1      |
|       | 22              | c.8909G>A                        | p.Trp2970Ter                         | stop_gained            | 1      |
|       | 23              | c.8991T>G                        | p.Tyr2997Ter                         | stop_gained            | 2      |
|       | 23              | c.9105T>G                        | p.Tyr3035Ter                         | stop_gained            | 1      |
|       | 23              | c.9076C>T                        | p.Gln3026Ter                         | stop_gained            | 1      |
|       |                 |                                  | stop_gained                          |                        |        |
|       | 25              | c.9431del                        | p.Ser3144LeufsTer19                  | frameshift             | 2      |

Table 2: Details of detected gBRCA1/2 pathogenic variants.

reimbursement and approval of gBRCA1/2 tests should be considered for this population in Korea. Although the prevalence of gBRCA1/2 PVs in patients with HR-positive, HER2-negative MBC without high-risk factors for gBRCA1/2 PVs was only 5.4%, the absolute number of patients with HR-positive, HER2-negative MBC without high-risk factors is not small. A more active gBRCA1/2 screening strategy should therefore reveal a larger number of gBRCA1/2 PV carriers. In our study, 19 out of 42 patients with an identified gBRCA1/2 PV did not meet the Korean reimbursement criteria for the gBRCA1/2 test, and screening in the unselected population nearly doubled the identified number of patients with a gBRCA1/2 PV.

In this study, we conducted a somatic mutation test using a multigene panel on 114 patients. We found that

2 patients without gBRCA PVs had somatic BRCA (sBRCA) PVs, while 5 patients exhibited PALB2 mutations. Recent studies have shown that PARP inhibitors are effective in patients with sBRCA or PALB2 mutations.<sup>23,24</sup> Based on this, recent ESMO NGS guidelines recommend testing for these genes in MBC using an ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score of IIB.<sup>7</sup> Our findings suggest that somatic testing for HRD genes using NGS may be valuable in Korean patients. All 7 patients with gBRCA PVs showed the same BRCA mutation in somatic tests. This indicates that somatic multigene sequencing could serve as an alternative diagnostic tool for gBRCA in patients who cannot undergo germline testing due to local reimbursement issues in Korea, underscoring the importance of somatic NGS testing, including for HRD-related genes in MBC management.

The gBRCA2 mutation is associated with poor outcomes in HR-positive, HER2-negative BC.<sup>25,26</sup> In BRCA carriers, prognosis of HR-positive BC was not superior to that of HR-negative tumors.<sup>27–29</sup> In our study, the gBRCA1 mutation was associated with worse outcomes with CDK4/6-inhibitor treatment. Although our sample size is very small, requiring cautious interpretation, similar findings have been reported in previous studies<sup>30–34</sup> Safonov et al. reported that HRD promotes RB1 loss-of-function mutations, causing resistance to CDK4/6 inhibitors.<sup>35</sup>

A major limitation in this study is its cross-sectional nature, despite enrolling patients prospectively. The eligible patients were not limited to newly diagnosed cases and included all patients with metastatic HER2-negative BC receiving palliative systemic treatment. Selection bias was therefore inevitable as patients with long-term survival after diagnosis of metastatic disease were enriched in this study. This selection bias and small size influenced the survival results, warranting cautious interpretation. The median survival of this study was much longer than the median survival time of the general population with same subtype. The exact prevalence of gBRCA1/2 PVs may be influenced by this selection bias if mutational status was associated with prognosis. A second limitation is the selection bias from the reimbursement policy of gBRCA1/2 tests in Korea, which changed during the study period. Patients were enrolled during October 2019 and March 2022. On June 2020, reimbursement for gBRCA1/2 mutation testing was expanded to patients with TNBC diagnosed at the age of 40–60 years old. The investigators were not obligated to enroll every consecutive patient with HER2-negative metastatic cancer, and patients without known gBRCA1/2 results would have tended to be enrolled more. Due to the expanded reimbursement, TNBC patients with a known gBRCA1/2 status may have been enrolled less often in the current study, resulting in fewer TNBC patients and a lower estimated prevalence of gBRCA1 PVs. The proportion of HR-positive, HER2-negative BC patients in this

study is higher than that in the general population, and *gBRCA1* pathogenic mutation were found in only 10 patients. The relatively higher incidence (2 of 10 patients) experiencing copy number loss in *gBRCA1* in this study reflected selection bias, particularly regarding TNBC patients.

Our study demonstrated the size of the current underestimation of *gBRCA1/2* PVs in unselected Korean patients with HER2-negative MBC, and particularly in patients not a high risk of being an *gBRCA1/2* PV carrier. An active screening strategy in unselected HER2-negative MBC and expanded reimbursement policy should therefore be pursued to avoid missing a potential candidate for systemic treatment with PARP inhibitors. An exact role of HRD gene mutations, including *BRCA1/2*, as biomarkers of endocrine treatment outcomes, and the underlying mechanism between HRD and endocrine resistance should be investigated further.

#### Contributors

Study design: YHP and HKA. Enrollment and clinical care: HKA, JHK, S-JK, JS, MJK, KHJ, KEL, JL, SAK, YSC, JHB, IHP, H-JK, HJK, JYJ, JLL, YYC, KHP, J-YK, S-AI, and YHP. Formal analysis: HKA and YHP. Original draft: HKA and YHP. Writing-review and editing: All authors. All authors had full access to all data in the study. The corresponding author had final responsibility for the decision to submit for publication.

#### Data sharing statement

A data sharing plan was not included in the trial protocol and hence data sharing will be conditional upon receiving the approval of the Institutional Review Board. A data access agreement will be required for access.

#### Declaration of interests

HKA declares consulting fees from Gilead, Amgen, Roche, Takeda, Daewoong, Bayer, Lilly and Daiichi-Sankyo, ayment or honoraria for lectures, presentations, speakers, bureaus, or educational events from Eisai, Boryung, Lilly, LSK Korea, AstraZeneca, Yuhon, Pfizer, Novartis, Sanofi/Aventis, MSD, Boehringer Ingelheim, Celltrion and Daiichi-Sankyo. JS declares grants or contracts from Seagen, MSD, Roche, Pfizer, Novartis, AstraZeneca, Lilly, GSK, Boehringer Ingelheim, Sanofi, Daiichi-Sankyo, Quriient, Dragonfly, Eikon, Gilead, Celcuity, BMS, HLB Life Science, Sermonix Pharmaceuticals, Olema, Hanmi Pharm, Ildong Pharmaceutical, Samyang Holding to institution, stock or stock options of Daiichi-Sankyo of immediate family member. KHJ declares consulting fees from AstraZeneca, Gilead, Roche, Eisai, Pfizer, Daiichi-Sankyo, MSD and Novartis. JHK declares grants or contracts from Roche, Ono Pharmaceuticals Ltd. and Eisai to institution, consulting fees from AstraZeneca, Eisai, MSD, Everest Medicine and Roche, payment or honoraria for lectures, presentations, speakers, bureaus, or educational events from Roche Korea, AstraZeneca, Roche diagnostics, Lilly Korea and Amgen. S-AI declares grants or contracts from AstraZeneca, Eisai, Daiichi-Sankyo, Pfizer, Roche, Boryung Pharm, consulting fees from AstraZeneca, Eisai, Lilly, MSD, Novartis, Pfizer, Roche, GSK and Daiichi-Sankyo. YHP declares grants or contracts from MSD, Novartis, Pfizer, AstraZeneca, Roche, Gencurix and Inocras, consulting fees from AstraZeneca, MSD, Pfizer, Eisai, Lilly, Roche, Gilead, Daiichi-Sankyo, MENARINI, EVEREST and Novartis, payment or honoraria for lectures, presentations, speakers, bureaus, manuscript writing, or educational events from AstraZeneca, MSD, Pfizer, Roche, Lilly, Daiichi-Sankyo, Novartis, Gilead and Helsinn, support for attending meetings and/or travel from Gilead, AstraZeneca and Pfizer, participation on a DataSafety Monitoring Board or Advisory Board of

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#### Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.lanwpc.2025.101622>.

#### References

- 1 Park EH, Jung KW, Park NJ, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2021. *Cancer Res Treat.* 2024;56(2):357–371.
- 2 Stoppa-Lyonnet D. The biological effects and clinical implications of BRCA mutations: where do we go from here? *Eur J Hum Genet.* 2016;24(1):S3–S9.
- 3 Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med.* 2018;379(8):753–763.
- 4 Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med.* 2017;377(6):523–533.
- 5 Im SA, Gennari A, Park YH, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, staging and treatment of patients with metastatic breast cancer. *ESMO Open.* 2023;8(3).
- 6 Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer\*. *Ann Oncol.* 2021;32(12):1475–1495.
- 7 Mosele MF, Westphalen CB, Stenzinger A, et al. Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group. *Ann Oncol.* 2024;35(7):588–606.
- 8 Gradishar WJ, Moran MS, Abraham J, et al. Breast cancer, version 3.2024, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw.* 2024;22(5):331–357.
- 9 Wang SM. A global perspective on the ethnic-specific BRCA variation and its implication in clinical application. *J Natl Cancer Center.* 2023;3(1):14–20.
- 10 Liu Y, Wang H, Wang X, et al. Prevalence and reclassification of BRCA1 and BRCA2 variants in a large, unselected Chinese Han breast cancer cohort. *J Hematol Oncol.* 2021;14(1):18.
- 11 Sun J, Meng H, Yao L, et al. Germline mutations in cancer susceptibility genes in a large series of unselected breast cancer patients. *Clin Cancer Res.* 2017;23(20):6113–6119.
- 12 Kang E, Seong M-W, Park SK, et al. The prevalence and spectrum of BRCA1 and BRCA2 mutations in Korean population: recent update of the Korean Hereditary Breast Cancer (KOHBCA) study. *Breast Cancer Res Treat.* 2015;151:157–168.
- 13 Ryu JM, Choi HJ, Kim I, et al. Prevalence and oncologic outcomes of BRCA 1/2 mutations in unselected triple-negative breast cancer patients in Korea. *Breast Cancer Res Treat.* 2019;173(2):385–395.
- 14 Im S-A, Xu B, Li W, et al. Olaparib monotherapy for Asian patients with a germline BRCA mutation and HER2-negative metastatic breast cancer: OlympiAD randomized trial subgroup analysis. *Sci Rep.* 2020;10(1):8753.
- 15 Koh SJ, Ohsumi S, Takahashi M, et al. Prevalence of mutations in BRCA1 and homologous recombination repair genes and real-world standard of care of Asian patients with HER2-negative metastatic breast cancer starting first-line systemic cytotoxic chemotherapy: subgroup analysis of the global BREAKOUT study. *Breast Cancer.* 2022;29(1):92–102.
- 16 Abugattas J, Llacuachqui M, Allende YS, et al. Prevalence of BRCA1 and BRCA2 mutations in unselected breast cancer patients from Peru. *Clin Genet.* 2015;88(4):371–375.
- 17 Gomes MC, Costa MM, Borojevic R, et al. Prevalence of BRCA1 and BRCA2 mutations in breast cancer patients from Brazil. *Breast Cancer Res Treat.* 2007;103(3):349–353.

- 18 Hernandez JE, Llacuachqui M, Palacio GV, et al. Prevalence of BRCA1 and BRCA2 mutations in unselected breast cancer patients from medellin, Colombia. *Hered Cancer Clin Pract.* 2014;12(1):11.
- 19 Kurian AW, Ward KC, Howlader N, et al. Genetic testing and results in a population-based cohort of breast cancer patients and ovarian cancer patients. *J Clin Oncol.* 2019;37(15):1305–1315.
- 20 Li G, Guo X, Tang L, et al. Analysis of BRCA1/2 mutation spectrum and prevalence in unselected Chinese breast cancer patients by next-generation sequencing. *J Cancer Res Clin Oncol.* 2017;143(10):2011–2024.
- 21 Malone KE, Daling JR, Doody DR, et al. Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. *Cancer Res.* 2006;66(16):8297–8308.
- 22 O'Shaughnessy J, Brezden-Masley C, Cazzaniga M, et al. Prevalence of germline BRCA mutations in HER2-negative metastatic breast cancer: global results from the real-world, observational BREAKOUT study. *Breast Cancer Res.* 2020;22(1):114.
- 23 Tung NM, Robson ME, Ventz S, et al. Tbcrc 048: phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. *J Clin Oncol.* 2020;38(36):4274–4282.
- 24 Gruber JJ, Afghahi A, Timms K, et al. A phase II study of talazoparib monotherapy in patients with wild-type BRCA1 and BRCA2 with a mutation in other homologous recombination genes. *Nat Cancer.* 2022;3(10):1181–1191.
- 25 Vidarsdottir L, Olafsdottir EJ, Barkardottir RB, et al. Estrogen receptor-positive breast cancer and adverse outcome in BRCA2 mutation carriers and young non-carrier patients. *NPJ Breast Cancer.* 2023;9(1):95.
- 26 Frenel JS, Lusque A, Delaloge S, et al. Efficacy of front-line treatment for hormone receptor-positive HER2-negative metastatic breast cancer with germline BRCA1/2 mutation. *Br J Cancer.* 2023;128(11):2072–2080.
- 27 Arecco L, Bruzzone M, Bas R, et al. Impact of hormone receptor status and tumor subtypes of breast cancer in young BRCA carriers. *Ann Oncol.* 2024;35(9):792–804.
- 28 Evans DG, Phillips K-A, Milne RL, et al. Survival from breast cancer in women with a BRCA2 mutation by treatment. *Br J Cancer.* 2021;124(9):1524–1532.
- 29 Lambertini M, Ceppi M, Hamy A-S, et al. Clinical behavior and outcomes of breast cancer in young women with germline BRCA pathogenic variants. *NPJ Breast Cancer.* 2021;7(1):16.
- 30 Collins JM, Nordstrom BL, McLaurin KK, et al. A real-world evidence study of CDK4/6 inhibitor treatment patterns and outcomes in metastatic breast cancer by germline BRCA mutation status. *Oncol Ther.* 2021;9(2):575–589.
- 31 Bruno L, Ostinelli A, Waisberg F, et al. Cyclin-dependent kinase 4/6 inhibitor outcomes in patients with advanced breast cancer carrying germline pathogenic variants in DNA repair-related genes. *JCO Precis Oncol.* 2022;6:e2100140.
- 32 Park SY, Suh KJ, Lee DW, et al. Prognostic role of tumor subtype and germline BRCA mutation in advanced breast cancer patients treated with palbociclib plus endocrine therapy. *Breast Cancer Res Treat.* 2022;196(1):121–128.
- 33 Lee S, Park K, Kim GM, et al. Exploratory analysis of biomarkers associated with clinical outcomes from the study of palbociclib plus endocrine therapy in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer. *Breast.* 2022;62:52–60.
- 34 Park YH, Im S-A, Park K, et al. Longitudinal multi-omics study of palbociclib resistance in HR-positive/HER2-negative metastatic breast cancer. *Genome Med.* 2023;15(1):55.
- 35 Safonov A, Bandlamudi C, de Lara PT, et al. Abstract GS4-08: comprehensive genomic profiling of patients with breast cancer identifies germline-somatic interactions mediating therapy resistance. *Cancer Res.* 2022;82(4\_Supplement):GS4-08.