Evaluating the relevance of germline BRCA mutation testing for breast cancer patients in Korea

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Evaluating the relevance of germline BRCA mutation testing for breast cancer patients in Korea

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It took me far longer than I had hoped to complete my master's program. While various factors played a role – the challenges of a demanding teaching career, the unforeseen and prolonged political turmoil, and my declining health – I ultimately believe the main reason was my own lack of diligence, and I deeply reflect on this. I sincerely hope that my doctoral journey will be much smoother than my master's.

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ABSTRACT

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Introduction

Since the introduction of insurance coverage for germline BRCA (gBRCA) mutation testing in Korea in August 2005, the screening criteria have expanded, leading to a significant rise in the number of patients tested. However, questions about the relevance of the gBRCA mutation testing under the current gBRCA screening criteria highlight the need for validation. This study aimed to evaluate the prevalence of gBRCA mutations in patients tested under current gBRCA screening criteria and assess the relevance of the gBRCA mutation testing.

Materials and methods

We performed a retrospective analysis of breast cancer patients at Gangnam Severance Hospital who underwent gBRCA mutation testing based on the gBRCA screening criteria established in June 2020. Next-generation sequencing was employed to identify gBRCA mutations.

Results

Between June 2020 and October 2023, 1,357 patients underwent gBRCA mutation testing under the expanded criteria. The overall mutation prevalence was 7.37% (100 of 1,357). Prevalence varied by the number of criteria met: 34.48% (20/58) for three or more criteria, 12.97% (38/293) for two criteria, and 4.17% (42/1,006) for one criterion. Among patients meeting only one criterion, clinically significant mutation prevalence was observed only in those with a family history of ovarian cancer.

Conclusions

The prevalence of gBRCA mutations in Korean breast cancer patients tested under current gBRCA screening criteria was lower than anticipated. These findings raise questions about the relevance of routinely performing gBRCA mutation testing for all patients meeting at least one gBRCA screening criterion.

Key words: germline BRCA, BRCA mutations, screening criteria, prevalence, breast cancer

1. Introduction

Approximately 5-10% of all breast cancers are attributable to hereditary factors [1, 2], primarily associated with germline mutations in the BRCA1 and BRCA2 genes [3-5]. For carriers of germline BRCA (gBRCA) mutations, the cumulative risk of developing breast cancer by age 80 is 72% for BRCA1 and 69% for BRCA2 [6]. A study conducted in Korea found that individuals with gBRCA mutations have a cumulative breast cancer risk of about 70% by age 70 [7].

Since the implementation of insurance coverage for gBRCA mutation testing in August 2005, the gBRCA screening criteria in Korea have gradually expanded. Initially, eligible patients included those with a family history of breast or ovarian cancer, individuals with family members who were gBRCA mutation carriers, and patients with high-risk factors such as early-onset breast cancer (age < 40), male breast cancer, bilateral breast cancer, or those diagnosed with or having a history of ovarian cancer [8]. However, following findings from the Korean Hereditary Breast Cancer (KOHBRA) study group and additional international research identifying high-prevalence subgroups of gBRCA mutations, the gBRCA screening criteria were expanded twice: first in May 2012 and again in June 2020, to encompass a broader population of candidates for testing [9-11].

In 2013, the highly publicized decision by actress Angelina Zolie to undergo bilateral prophylactic mastectomy after identifying a BRCA mutation drew global attention to gBRCA mutations, a phenomenon widely termed the “Angelia Zolie effect” [12, 13]. This increased awareness, together with the ongoing expansion of screening criteria, has been associated with a significant worldwide rise in the utilization of genetic testing. In Korea, the number of gBRCA mutation testing conducted in 2017 was over ten-fold higher than in 2010 [14]. Despite this substantial increase, concerns persist regarding the actual prevalence of gBRCA mutations detected in these expanded testing populations. Unnecessary testing may impose financial burdens on patients and lead to excessive costs for healthcare systems that cover these testing, as evidenced in Korea. Therefore, there is an urgent need to validate the existing gBRCA screening criteria, although data supporting such validations are currently limited. The aim of our study was to determine the actual prevalence of gBRCA mutations among Korean breast cancer patients subjected to these gBRCA screening criteria, by evaluating the relevance of current gBRCA mutation testing in selected group.

2. Materials and methods

2.1. Data collection

After Institutional Review Board approval (IRB no. 3-2024-0051), We retrospectively analyzed data from patients with invasive breast cancer or carcinoma *in situ* who underwent gBRCA mutation testing at Gangnam Severance Hospital between July 2020 and October 2023. Data collected included genetic information (results of gBRCA mutation testing), sex, age at diagnosis, family cancer history (defined as having at least one relative within the second-degree relatives (SDR) diagnosed with cancer), and clinicopathological information. Clinicopathological data encompassed tumor subtype, estrogen receptor (ER) and progesterone receptor (PR) expression, human epidermal growth factor receptor 2 (HER2) overexpression, and the presence of bilateral breast cancer. ER and PR status was determined from preoperative tissue samples, including core needle biopsy or fine needle aspiration, using immunohistochemistry. ER and PR positivity were defined as staining of more than 1% of tumor cell nuclei. HER2 status was evaluated according to the 2013 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines [15]. HER2 status was assessed following the recommendation of the 2013 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) [16]. TNBC was defined as ER and PR-negative and lacking HER2 overexpression. Considering the retrospective approach, consent from patient was waived for this study.

2.2. gBRCA screening criteria for gBRCA mutation testing

In Korea, insurance coverage for gBRCA mutation testing was introduced in 2005. Due to significant cost differences for patients depending on insurance coverage, clinical practice has closely aligned with the insurance coverage criteria. Consequently, the gBRCA screening criteria have evolved alongside revisions to insurance guidelines for gBRCA mutation testing

As of June 2020, the revised gBRCA screening criteria for breast cancer patients are as follows: (A) early-onset breast cancer (diagnosed at age ≤ 40 without additional risk factors), (B) family history of breast cancer, (C) family history of ovarian cancer, (D) family history of pancreatic cancer, (E) family history of prostate cancer (a family history of cancer is defined as at least one relative within SDR diagnosed with cancer), (F) TNBC diagnosed at age ≤ 60 without additional risk factors, (G) bilateral breast cancer, (H) male breast cancer, (I) concurrent diagnosis of ovarian or pancreatic cancer, and (J) the presence of at least one gBRCA mutation carrier within SDR. Insurance coverage

for gBRCA mutation testing is provided to individuals meeting at least one of these criteria.

Our analysis focused on patients meeting eight criteria (A-H). The rationale of excluding criteria (I) and (J) was the limited number of patients tested due to concurrent ovarian or pancreatic cancer or the presence of a gBRCA mutation carrier in their family. Newly added criteria in our analysis compared to previous guidelines included a family history of pancreatic cancer, a family history of prostate cancer, and TNBC diagnosed at ages 41-60. Among patients with TNBC diagnosed at age ≤ 60, those diagnosed at age ≤ 40 met the pre-existing criterion for early-onset breast cancer and were eligible for gBRCA mutation testing under earlier screening guidelines. Thus, TNBC patients diagnosed between the ages of 41 and 60 constitute a newly included cohort under the updated screening criteria.

In analysis limited to patients meeting a single gBRCA screening criterion, TNBC patients diagnosed at ages 41-60 were evaluated separately from those meeting the early-onset breast cancer criterion. Notably, TNBC patients diagnosed at age ≤ 40 meet two criteria: early-onset breast cancer and TNBC diagnosed at age ≤ 60.

2.3. Selection of candidates for gBRCA mutation testing

The molecular subtype of the tumor was determined for all patients in this study using biopsy specimens. For patients who had undergone biopsy at an external facility prior to their visit, tissue specimens were submitted to our institution's pathology department for re-evaluation, ensuring centralized and standardized pathologic results. Accurate molecular subtype confirmation is crucial, as the gBRCA screening criteria include patients without additional risk factors up to age 40 for other subtypes but up to age 60 for TNBC.

At the initial visit to the Breast Cancer Center, patients undergo comprehensive history-taking, with a focus on personal medical and family cancer histories. gBRCA mutation testing is systematically offered to patients who meet the established screening criteria. Additionally, patients undergoing gBRCA mutation testing receive genetic counseling through collaborative consultations at the Breast Cancer Precision Medicine Center. This center specializes in assessing familial and hereditary cancer risks and provides comprehensive strategies for early detection and prevention of hereditary cancers. The Breast Cancer Precision Medicine Center conducts detailed history-taking through consultations with physicians trained in genetic counseling, identifying personal and family medical histories that may have been previously overlooked at the Breast Cancer Center. These efforts aim to minimize the number of patients requiring gBRCA mutation testing who may not have been appropriately screened, enhancing the overall accuracy and relevance of the testing process.

2.4. Detection and interpretation of gBRCA mutation

Next-generation sequencing (NGS) was performed on blood samples to detect gBRCA mutations using the NextSeq 550 System (Illumina; NGS Wet process; ver. IlluminaNGS-E1-20200601). Quality control, sequence variant analysis, and copy number variant analysis were conducted using the NGS Dry Process (ver. Illumina NGS-E3-20230920). Variant analysis and annotation were carried out using multiple database, including the Online Mendelian Inheritance in Man (OMIM), Human Gene Mutation Database (HGMD), ClinVar, dbSNP 1000 Genome, the Exome Aggregation Consortium (ExAC), and the Exome Sequencing Project (ESP). Reference sequences were based on GeneBank Accession number(s) (build GRCh37, hg19), and variants were named following the Human Genome Variation Society (HGVS) nomenclature guidelines (https://hgvs.org, assessed November 23, 2024).

Variants were interpreted and classified according to the 2015 American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology (AMP) and ClinGen guidelines [17]. Based on these criteria, variants were stratified as pathogenic, likely pathogenic, uncertain significance, likely benign, and benign. Variants classified as pathogenic or likely pathogenic (PV/LPV) were considered mutations, while those categorized as variants of uncertain significance, likely benign, or benign were deemed no mutations.

2.5. Statistical analysis

The primary objective of this study was to evaluate the relevance of current gBRCA mutation testing by determining the prevalence of gBRCA mutations among patients tested under the gBRCA screening criteria. Using the 10% prevalence benchmark for genetic mutations specified in the NICE guidelines [18], the study aimed to assess whether a similar prevalence was observed in the study cohort. Additionally, patients were categorized based on the number of applicable gBRCA screening criteria to evaluate prevalence within subgroups.

Chi-square tests were used to compare the distribution of patients meeting each gBRCA screening criterion across groups stratified by gBRCA mutation status. A p-value of less than 0.05 was considered statistically significant. All statistical analyses and figure generation were performed using SPSS version 28.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism software version 10 (GraphPad Software Inc., MA, USA).

3. Results

3.1. Patient cohort and distribution of gBRCA screening criteria

Between July 2020 and October 2023, 1,364 patients at Gangnam Severance Hospital underwent gBRCA mutation testing following a diagnosis of invasive carcinoma or carcinoma *in situ* under the gBRCA screening criteria. Seven patients were excluded from the analysis: two were tested due to the presence of a gBRCA mutation carrier within SDR, three underwent testing at the discretion of their physician for clinical research enrollment, one had an indeterminate gBRCA mutation status, and one underwent testing upon patient request despite not meeting the screening criteria. Consequently, the analysis cohort included 1,357 patients (Figure 1), all of whom were Korean breast cancer patients, except for one Russian woman.

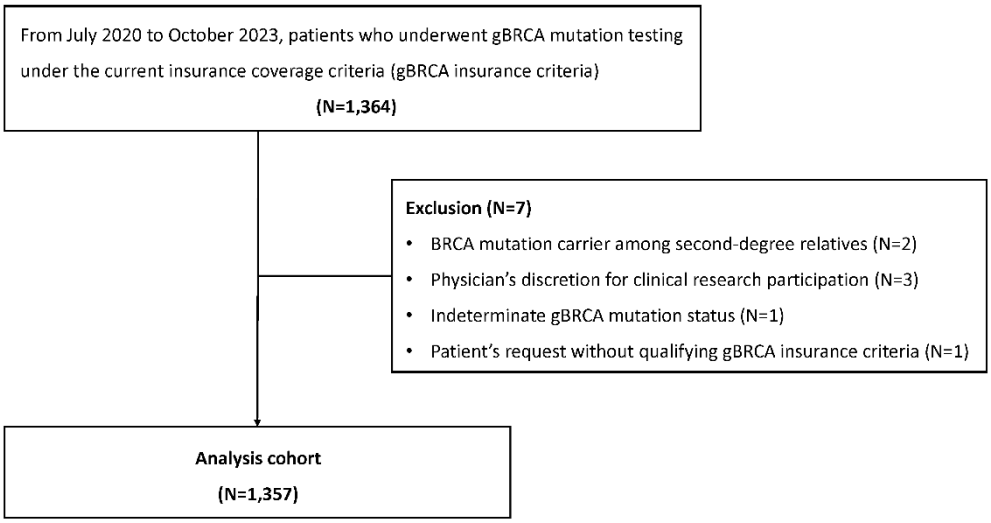

Figure 1. Consort diagram

Table 1 summarizes the distribution of patients meeting each gBRCA screening criterion stratified by gBRCA mutation status. In the PV/LPV group, patients were significantly more likely to have a family history of breast cancer (56.0% vs. 39.8%; $p = 0.001$), ovarian cancer (13.0% vs. 3.6%; $p < 0.001$), and pancreatic cancer (20.0% vs. 10.2%; $p = 0.002$), and to have TNBC diagnosed at age ≤ 60 (46.0% vs. 22.9%; $p < 0.001$) compared with the no PV/LPV group. In contrast, there were no significant differences between the groups for early-onset breast cancer (41.0% vs. 33.7%; $p = 0.143$) and a family history of prostate cancer (4.0% vs. 6.2%; $p = 0.374$). Interestingly, the proportion of patients with bilateral breast cancer was higher in the no PV/LPV group (3.0% vs. 9.1%; $p = 0.038$). Among the 15 male breast cancer patients, no gBRCA mutations were identified, making statistical comparisons between groups insignificant (0% in the PV/LPV group vs. 1.2% in the no PV/LPV group; $p = 0.617$).

Table 1. The distribution of gBRCA screening criteria by gBRCA mutation status

Variables, N (%)	PV/LPV (N=100)	No PV/LPV (N=1257)	*p*-value
Early-onset breast cancer			0.143
Yes	41 (41.0)	423 (33.7)	
No	59 (59.0)	834 (66.3)	
Family history of breast cancer			0.001
Yes	56 (56.0)	500 (39.8)	
No	44 (44.0)	757 (60.2)	
Family history of ovarian cancer			< 0.001
Yes	13 (13.0)	45 (3.6)	
No	87 (87.0)	1,212 (96.4)	
Family history of pancreatic cancer			0.002
Yes	20 (20.0)	128 (10.2)	
No	80 (80.0)	1,129 (89.8)	
Family history of prostate cancer			0.374
Yes	4 (4.0)	78 (6.2)	
No	96 (96.0)	1,179 (93.8)	
TNBC diagnosed at age ≤ 60			< 0.001
Yes	46 (46.0)	288 (22.9)	
No	54 (54.0)	969 (77.1)	
Bilateral breast cancer			0.038
Yes	3 (3.0)	114 (9.1)	
No	97 (97.0)	1,143 (90.9)	
Male breast cancer			0.617
Yes	0	15 (1.2)	
No	100 (100.0)	1,242 (98.8)	

In this table, patients meeting multiple gBRCA screening criteria were included in each relevant criterion group, allowing for overlap across categories
Abbreviation, TNBC, triple-negative breast cancer

3.2. Prevalence of gBRCA mutations in the overall cohort

Of the 1,357 patients analyzed, 100 were identified as gBRCA mutation carriers, resulting in an overall prevalence of 7.37% (100/1,357). The prevalence of gBRCA mutations was further assessed within subgroups defined by each gBRCA screening criterion. Among 464 patients with early-onset breast cancer, the prevalence was 8.84% (41/464). In the subgroup with a family history of breast cancer (N=555), the prevalence was 10.07% (56/555). Patients with a family history of ovarian cancer had the highest prevalence at 22.41% (13/58). For those with a family history of pancreatic cancer, the prevalence was 13.51% (20/148). Among 82 patients with a family history of prostate cancer, the prevalence was 4.88% (4/82). In the TNBC diagnosed at age ≤ 60 (N=334), the prevalence was 13.77% (46/334). Among 117 patients with bilateral breast cancer, the prevalence was 2.56% (3/117). No gBRCA mutations were identified among the 15 male breast cancer patients in the cohort (Table 2).

Table 2. Prevalence of gBRCA mutation in subgroups corresponding to each criterion (including overlapping case)

N (%)	A	B	C	D
PV/LPV	41 (8.84)	56 (10.07)	13 (22.41)	20 (13.51)
No PV/LPV	423	500	45	128
Total	464	556	58	148

(Continued)

N (%)	E	F	G	H
PV/LPV	4 (4.88)	46 (13.77)	3 (2.56)	0
No PV/LPV	78	288	114	15
Total	82	334	117	15

Appendix) A. early-onset breast cancer, B. family history of breast cancer, C. family history of ovarian cancer, D. family history of pancreatic cancer, E. family history of prostate cancer, F. triple-negative breast cancer diagnosed at age ≤ 60, G. bilateral breast cancer, H. male breast cancer
Abbreviation, PV/LPV, pathogenic variants/likely pathogenic variants

3.3. Prevalence of gBRCA mutations by the number of gBRCA screening criteria met

Next, we categorized patients by the number of applicable gBRCA screening criteria, and the prevalence of gBRCA mutations was evaluated within each subgroup. The majority of patients (74.13%; 1,006/1,357) met only one screening criterion, with a low prevalence of 4.17% (42/1,006). Among the 351 patients meeting two or more criteria, the prevalence was 16.52% (58/351), exceeding the clinical significance threshold of 10%. Notably, patients meeting three or more criteria exhibited a particularly high prevalence of 34.48% (20/58). Figure 2 illustrates the prevalence of gBRCA mutations according to the number of applicable gBRCA screening criteria.

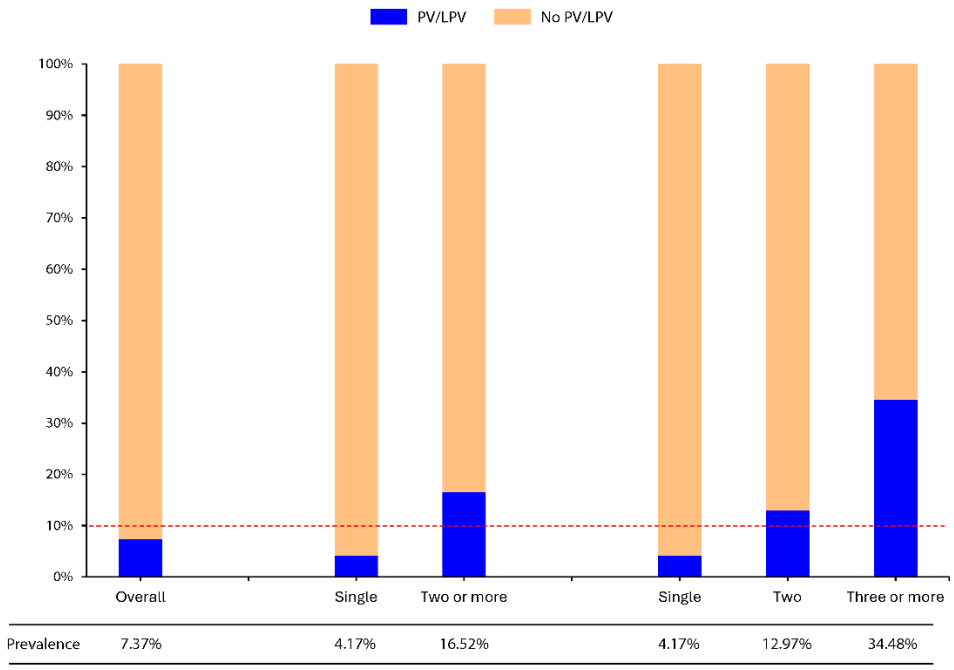

Figure 2. Prevalence of gBRCA mutations according to the number of applicable gBRCA screening criteria

3.4. Prevalence of gBRCA mutations in patients meeting two screening criteria

Given the substantial prevalence of gBRCA mutation observed in the patient population meeting three or more gBRCA screening criteria, the relevance of gBRCA mutation testing in this cohort is well established. To evaluate the relevance of gBRCA mutation testing for patients meeting fewer criteria, we focused on those who met two or one screening criterion. To avoid overlap with early-onset breast cancer, the criterion for "TNBC diagnosed at age ≤ 60" was adjusted to "TNBC diagnosed at ages 41-60" during the categorization and analysis.

Among 293 patients meeting two of the gBRCA screening criteria, gBRCA mutations were detected in 38 cases, yielding a prevalence of 12.97% (38 of 293), which exceeds the 10% benchmark. Table 3 presents the prevalence of gBRCA mutations in subgroups categorized by the combinations of the criteria within this subgroup. The prevalence varied significantly across combinations of criteria. Some combinations showed high mutation rates, while others revealed lower rates or no mutations at all. These findings suggest that gBRCA mutation testing may not be uniformly relevant for all patients meeting two criteria and highlight the need to identify combinations associated with a higher prevalence.

Table 3. Prevalence of gBRCA mutations according to combinations within the subgroup that applicable two of the gBRCA screening criteria

N	A+B	A+C	A+D	A+E	A+F	A+G	A+H
PV/LPV	11	0	1	1	3	0	0
No PV/LPV	56	3	16	8	38	0	0
Total	67	3	17	9	41	0	0
Prevalence (%)	16.42	0	5.88	11.11	7.32	0	0

(Continued)

N	B+C	B+D	B+E	B+F	B+G	B+H	C+D
PV/LPV	1	6	0	10	2	0	0
No PV/LPV	7	19	15	31	5	1	2
Total	8	25	15	41	7	1	2
Prevalence (%)	12.5	24	0	24.39	28.57	0	0

(Continued)

N	C+E	C+F	C+G	C+H	D+E	D+F	D+G
PV/LPV	0	0	0	0	0	0	1
No PV/LPV	3	2	0	0	7	15	6
Total	3	2	0	0	7	15	7
Prevalence (%)	0	0	0	0	0	0	14.29

(Continued)

N	D+H	E+F	E+G	E+H	F+G	F+H	G+H
PV/LPV	0	1	0	0	0	0	0
No PV/LPV	0	9	4	0	5	0	0
Total	0	10	4	0	5	0	0
Prevalence (%)	0	10	0	0	0	0	0

Appendix) A. early-onset breast cancer, B. family history of breast cancer, C. family history of ovarian cancer, D. family history of pancreatic cancer, E. family history of prostate cancer, F. triple-negative breast cancer diagnosed at age ≤ 60, G. bilateral breast cancer, H. male breast cancer

Abbreviation, PV, pathogenic variants; LPV, likely pathogenic variants

3.5. Subgroup analysis of patients applicable only a single gBRCA screening criterion

Most patients underwent gBRCA mutation testing based on only one screening criterion, underscoring the importance of evaluating the relevance of testing in this population.

We analyzed the prevalence of gBRCA mutations within subgroups based on each gBRCA screening criterion. Among the 287 patients with early-onset breast cancer, the prevalence of gBRCA mutations was 4.53% (13/287). In the subgroup with a family history of breast cancer, which included 341 patient, 2.64% (9/341) had confirmed gBRCA mutations. For patients with family history of ovarian cancer, 21 met this criterion, yielding a mutation prevalence of 19.05% (4 of 21). Among the 51 patients with a family history of pancreatic cancer, the prevalence was 3.92% (2/51), while in the 183 patients classified as TNBC diagnosed at ages 41-60, the prevalence of gBRCA mutations was 7.65% (14/183). No gBRCA mutations were detected among patients with a family history of prostate cancer, bilateral breast cancer, or male breast cancer (Table 4).

Table 4. Prevalence of gBRCA mutations corresponding to each criterion within the subgroup that met only one criterion of the gBRCA screening criteria

N (%)	A	B	C	D
PV/LPV	13 (4.53)	9 (2.64)	4 (19.05)	2 (3.92)
No PV/LPV	274	332	17	49
Total	287	341	21	51

(Continued)

N (%)	E	F	G	H
PV/LPV	0	14 (7.65)	0	0
No PV/LPV	20	169	89	14
Total	20	183	89	14

Appendix) A. early-onset breast cancer, B. family history of breast cancer, C. family history of ovarian cancer, D. family history of pancreatic cancer, E. family history of prostate cancer, F. triple-negative breast cancer diagnosed at ages 41-60, G. bilateral breast cancer, H. male breast cancer
Abbreviation, PV, pathogenic variants; LPV, likely pathogenic variants

3.6. Evaluating the relevance of gBRCA mutation testing through the analysis of gBRCA mutation prevalence

The analysis revealed significant variability in gBRCA mutation prevalence based on the number of gBRCA screening criteria met. To further assess the relevance of gBRCA mutation testing, we examined patient groups under different conditions.

First, we compared the prevalence of gBRCA mutations in patients meeting specific criteria with those lacking additional risk factors beyond the specified criterion (Figure 3). For most criteria, the prevalence among patients meeting the specified criterion was approximately 10%, consistent with clinical benchmarks, except for family history of prostate cancer, bilateral breast cancer, and male breast cancer. However, among patients without additional risk factors, the prevalence was significantly lower across all criteria except for family history of ovarian cancer.

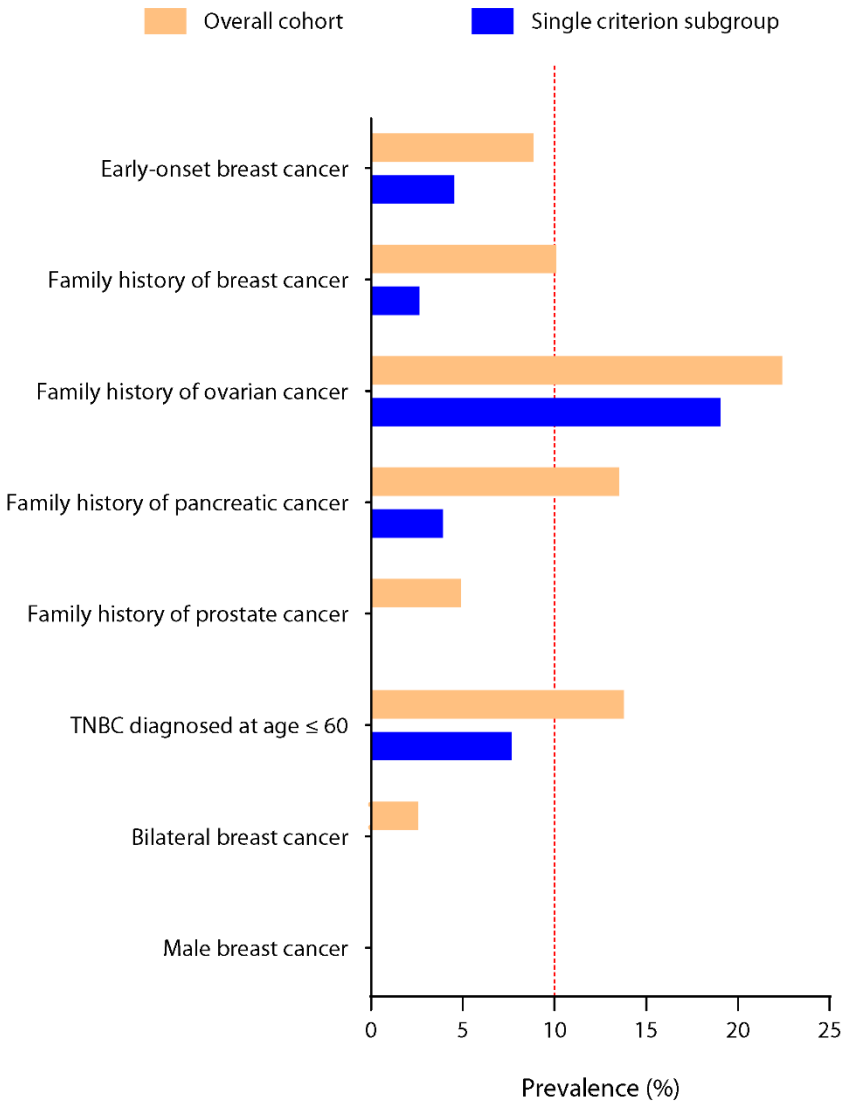

Figure 3. Comparison of gBRCA mutation prevalence corresponding to gBRCA screening criteria in the overall cohort and in the subgroup met only one criterion.

Appendix) Overall prevalence refers to the prevalence of gBRCA mutations among patients within the entire cohort who meet the specified gBRCA screening criteria. Single prevalence, on the other hand, denotes the prevalence of gBRCA mutations among patients who meet the specified gBRCA screening criteria but lack any additional risk factors.

When stratifying patient groups by the presence of absence of other risk factors, a prevalence exceeding 10% was observed for most criteria when additional risk factors were present. In contrast, as previously mentioned, the prevalence was low for all criteria in the absence of additional risk factors, except for family history of ovarian cancer. This pattern remained consistent for newly added criteria, including family history of pancreatic cancer, family history of prostate cancer, and TNBC diagnosed at ages 41-60 (Figure 4). Table 5 presents the prevalence of gBRCA mutations stratified by the presence or absence of additional risk factors.

Table 5. Prevalence of gBRCA mutations by other risk factors in patients meeting specific gBRCA screening criteria

Criterion	PV/LPV	No PV/LPV	Prevalence (%)
Early-onset breast cancer			
With other risk factors	28	149	15.82
Without other risk factors	13	274	4.53
Family history of breast cancer			
With other risk factors	47	168	21.86
Without other risk factors	9	332	2.64
Family history of ovarian cancer			
With other risk factors	9	28	24.32
Without other risk factors	4	17	19.05
Family history of pancreatic cancer			
With other risk factors	18	79	18.56
Without other risk factors	2	49	3.92
Family history of prostate cancer			
With other risk factors	4	58	6.45
Without other risk factors	0	20	0
TNBC diagnosed at ages 41-60			
With other risk factors	32	119	21.19
Without other risk factors	14	169	7.65
Bilateral breast cancer			
With other risk factors	3	25	10.71
Without other risk factors	0	89	0

Appendix) No gBRCA mutation carriers were found among male breast cancer patients, so this group is excluded from the table

Abbreviation, gBRCA, germline BRCA; PV, pathogenic variants; LPV, likely pathogenic variants; TNBC, triple-negative breast cancer

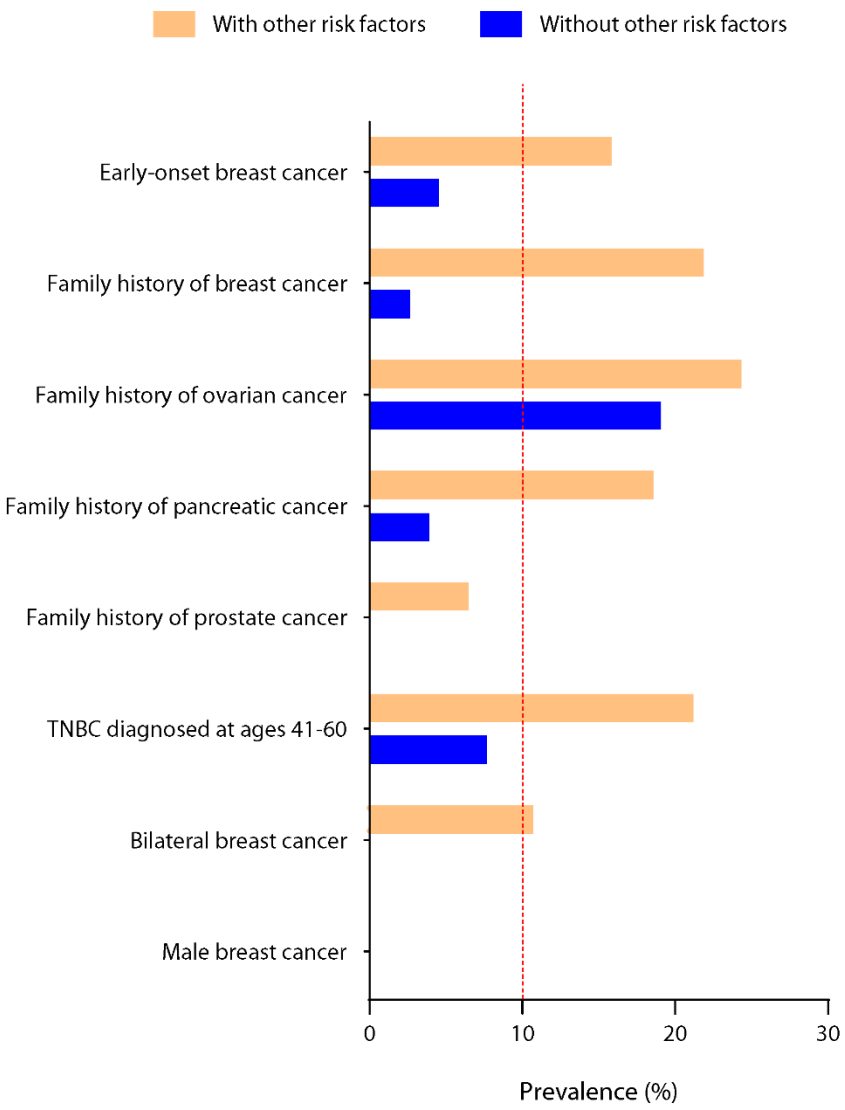

Figure 4. Prevalence of gBRCA mutations stratified by the presence or absence of other risk factors in patient groups meeting each specific gBRCA screening criteria

To assess the relevance of the gBRCA screening criteria for TNBC diagnosed at age ≤ 60, introduced in the June 2020 revision, we analyzed gBRCA mutation prevalence by the presence or absence of additional risk factors and by age at diagnosis. Table 6 reports the prevalence among TNBC patients aged 41-60 years without additional risk factors, whereas Table 7 details the prevalence among TNBC patients under 60 years with additional risk factors. Among TNBC patients under age 60, those without additional risk factors had a gBRCA mutation prevalence below 10%, regardless of age at diagnosis. In contrast, patients with additional risk factors consistently demonstrated a prevalence exceeding 10%, irrespective of diagnostic age.

These findings underscore that the prevalence of gBRCA mutations is low among patients meeting only one screening criterion but reaches clinically significant levels in patients meeting two or more criteria. Therefore, routine testing should be prioritized for patients meeting at least two criteria. However, for patients meeting only one criterion, the relevance of universal testing remains debatable, and further investigation is needed to refine the strategies of gBRCA mutation testing for this subgroup.

Table 6. Prevalence of gBRCA mutations in TNBC patients aged 41-60 without other risk factors.

Ages	PV/LPV	No PV/LPV	Total	Prevalence (%)
41-45	2	29	31	6.45
46-50	2	40	42	4.76
51-55	5	50	55	9.09
56-60	5	50	55	9.09
Total	14	169	183	7.65

Abbreviation, gBRCA, germline BRCA; PV, pathogenic variants; LPV, likely pathogenic variants

Table 7. Prevalence of gBRCA mutations in TNBC patients under the age of 60 with other risk factors

Ages	PV/LPV	No PV/LPV	Total	Prevalence (%)
≤ 40	13	49	62	20.97
41-45	6	16	22	27.27
46-50	4	14	18	22.22
51-55	4	18	22	18.18
56-60	3	13	16	18.75
Total	30	110	140	21.43

Abbreviation, gBRCA, germline BRCA; PV, pathogenic variants; LPV, likely pathogenic variants

4. Discussion

This study evaluated the prevalence of gBRCA mutations in Korean breast cancer patients tested under gBRCA screening criteria implemented since July 2020. The overall prevalence was less than 10%, driven primarily by the low prevalence among patients who met only a single gBRCA screening criterion, a group that comprised most of the cohort. In contrast, the prevalence exceeded 10% in patients meeting two or more criteria. These findings underscore the relevance of gBRCA mutation testing in patients with multiple risk factors but also reveal that its utility may not be consistently warranted in patients meeting only a single criterion.

Advances in breast cancer treatment have identified new therapeutic targets, including gBRCA mutations. Mutations in BRCA gene disrupt DNA repair pathways, increasing breast cancer risk [19, 20]. The proven efficacy of poly (ADP-ribose) polymerase (PARP) inhibitors in gBRCA-mutated tumors highlights the critical need for accurate testing to identify eligible patients for targeted therapies [21-24].

In Korea, the costs of genetic testing vary significantly based on insurance coverage, leading to alignment between gBRCA screening criteria and reimbursement guidelines. Since 2005, these criteria have progressively expanded, increasing testing volumes. However, this expansion has also escalated financial burdens on the national healthcare system, highlighting the need for cost-effectiveness evaluations. While there have been calls to further expand testing criteria, studies assessing the clinical relevance of gBRCA mutation testing in Korea remain limited.

This study revealed significantly lower gBRCA mutation prevalence among patients meeting only one screening criterion compared to those meeting two or more. This trend extended to newly added criteria, such as a family history of pancreatic or prostate cancer and TNBC diagnosed at ages 41-60. Although BRCA mutations are associated with pancreatic and prostate cancers [10, 11], our findings suggest that these family histories may not significantly increase mutation likelihood in Korean breast cancer patients. Many research also highlight limited evidence supporting these associations, underscoring the need to consider additional clinical factors, such as age at diagnosis, metastatic status, and other risk factors, when evaluating the relevance of screening criteria [25-27].

For TNBC, a cumulative mutation prevalence exceeding 10% in patients aged ≤ 60 led to the inclusion of this group in the screening criteria [9]. However, the study also reported a mutation prevalence below 10% in TNBC patients aged 41-60 without additional risk factors, consistent with our findings. These results raise important questions about the relevance of universal insurance coverage for gBRCA mutation testing in this subgroup.

Of course, the findings of our study alone cannot conclude that gBRCA mutation testing is irrelevant in the majority of breast cancer patients in Korea who meet only a single gBRCA screening

criterion. Data from the KOHBRA study, which evaluated the prevalence of BRCA mutations in Korean breast cancer patients, demonstrated a prevalence of approximately 10% not only in individuals with two or more risk factors but also in those meeting specific gBRCA screening criteria, such as a family history of breast cancer, bilateral breast cancer, or early-onset breast cancer [28]. Our research was conducted as a single-institution, retrospective study with a relatively small sample size, making it inherently susceptible to limitations such as confounding factors and selection bias. These factors inevitably affect the strength of the analysis. Nevertheless, a key strength of our study is its contribution to understanding the relevance of gBRCA mutation testing, particularly given the limited data available in Korea on the prevalence of gBRCA mutations in patients undergoing testing based on established screening criteria. Assessing the cost-effectiveness of genetic testing requires threshold analyses and regular updates on testing costs [29]. In this regard, studies like ours, which use real-world data to analyze the prevalence of gBRCA mutations in selected populations, are essential. Given the paucity of such studies in Korea, our findings underscore the need for further validation and highlight the importance of conducting large-scale cohort studies to fill this gap. We hope that this study serves as a catalyst for future research aimed at optimizing genetic testing strategies and addressing unmet clinical needs.

Beyond the previously noted limitations related to study design and cohort size, this study has several additional limitations. First, the analysis relied solely on mutation prevalence to assess relevance, without incorporating economic metrics such as testing costs or quality-adjusted life years (QALYs) [30, 31]. As cost-effectiveness evaluations require a multifaceted approach, the reliance on prevalence data alone limits the evidence supporting the relevance of gBRCA mutation testing. Second, data obtained through patient and caregiver history-taking are prone to inaccuracies due to reliance on memory. Additionally, the limited data collection represents a notable limitation, as it hindered further studies to identify subgroups within the cohort where the relevance of gBRCA mutation testing could be established. International guidelines such as the National Comprehensive Cancer Network (NCCN) guideline (ver 2.2025) and related studies propose more detailed genetic testing criteria for high-risk susceptibility genes compared to the gBRCA screening criteria used in Korea. For instance, many guidelines define a family history of breast cancer as having at least one relative diagnosed before age 50 or two relatives within SDR [32-34]. Our study lacked detailed information, such as clinicopathological data of family members diagnosed with cancers or the age of cancer onset in patients with bilateral breast cancer, limiting the depth of our analyses. Future studies should prioritize the collection and analysis of such data to develop more personalized screening criteria for Korean breast cancer patients.

5. Conclusion

The prevalence of gBRCA mutations among Korean breast cancer patients tested under current insurance coverage criteria for gBRCA mutation testing was lower than expected. Although testing is clinically relevant for high-risk patients meeting two or more criteria, the low prevalence observed in patients meeting only a single criterion raises questions about the appropriateness of universal insurance coverage for gBRCA mutation testing in this subgroup. Refining gBRCA screening criteria to better align with the clinical profiles of Korean patients and revising insurance coverage policies are essential. Large-scale cohort studies will be critical to guide and validate these refinements.

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Abstract in Korean

한국 유방암 환자를 대상으로 한 유전성 BRCA 돌연변이 검사의 효용성 평가

본 논문은 현재 한국에서 사용되고 있는 유전성 BRCA 돌연변이 검사의 보험 급여 기준에 따라 검사를 시행한 국내 유방암 환자들에서 유전성 BRCA 돌연변이의 빈도를 평가한 연구이다. 한국에서는 검사의 보험 급여 적용 여부에 따라 검사비의 차이가 크기 때문에 임상적으로 유전성 BRCA 돌연변이 검사의 보험 급여 기준을 스크리닝 기준으로 사용하고 있다. 최근 유전성 BRCA 돌연변이에 대한 관심이 높아지면서 현재 시행되는 유전성 BRCA 돌연변이 검사의 효용성에 대한 관심은 증가하고 있으나 이에 대해 평가한 연구는 많지 않았기 때문에 본 연구를 디자인하게 되었다.

우리는 2020 년 7 월 이후로 개정된 유전성 BRCA 돌연변이 스크리닝 기준에 따라 강남세브란스병원에서 유전성 BRCA 돌연변이 검사를 시행한 유방암 환자들의 데이터를 후향적으로 수집하여 분석하였다. 유전성 BRCA 돌연변이를 확인하기 위해 차세대 염기서열 분석 (Next-generation sequencing, NGS)을 사용하였다.

2020 년 7 월부터 2023 년 10 월까지 유전성 BRCA 돌연변이 검사를 시행한 1,357 명 중 유전성 BRCA 돌연변이의 빈도는 7.37% (100/1,357)이었다. 빈도는 해당하는 criteria 의 개수에 따라 달랐는데 3 개 이상 해당하는 환자군에서의 빈도는 34.48% (20/58), 2 개 해당하는 환자군에서의 빈도는 12.97% (38/293), 그리고 1 개만 해당하는 환자군에서의 빈도는 4.17% (42/1,006)였다. 유전성 BRCA 스크리닝 기준 중 1 개만 해당하는 환자군에서는 난소암 가족력에 해당하는 환자군 외에는 임상적으로 유의한 유전성 BRCA 돌연변이 빈도가 확인되지 않았다.

결론적으로 현재의 유전성 BRCA 스크리닝 기준에 따라 검사를 시행한 한국 유방암 환자에서의 유전성 BRCA 돌연변이의 빈도는 기대했던 것보다 높지 않았다. 본 연구의 결과는 현재 1 개 이상의 기준에 해당하는 모든 환자들에서 유전성 BRCA 돌연변이 검사를 시행하는 것에 대한 효용성에 대한 재고가 필요할 수 있음을 암시하는 결과이다.

핵심되는 말 : 유전성 BRCA, BRCA 돌연변이, 스크리닝 기준, 빈도, 유방암