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CLINICAL TRIAL

Prevalence and oncologic outcomes of *BRCA 1/2* mutations in unselected triple-negative breast cancer patients in Korea

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Abstract

Purpose Triple-negative breast cancer (TNBC) accounts for 10–20% of all diagnosed BCs and it is enriched in *BRCA1* mutation. Guidelines for Western countries suggest that *BRCA 1/2* genetic testing should be done for patients with TNBC diagnosed less than 60 years, but there is lack of evidence supporting genetic testing in Asian populations. We determined the prevalence of germline *BRCA 1/2* mutations among unselected Korean patients with TNBC and analyzed oncologic outcomes.

Methods From among 1628 women with TNBC who underwent surgery at Samsung Medical Center (SMC) between Jul 2008 and Jan 2016, 999 samples were available in the SMC biobank for testing germline *BRCA 1/2* mutations using next-generation DNA sequencing.

Results Overall, 131 Korean patients (13.1%) had *BRCA 1/2* mutations: 97 (9.7%) were in *BRCA 1*, and 35 (3.5%) were in *BRCA 2*. One patient had both *BRCA 1* and *BRCA 2* mutations. Overall, 68 distinct pathologic or likely pathogenic variants (43 *BRCA1* and 25 *BRCA2*) were found. Among those diagnosed at ≤ 60 years, the prevalence of *BRCA 1/2* mutation was 14.5%. The mean age of diagnosis of *BRCA1/2* mutation carriers was significantly younger than that of non-carriers (45.6 vs. 50.1 years, $p < 0.0001$). The median follow-up duration was 53.6 months. There were no significant differences in disease-free survival, overall survival, or breast cancer-specific survival ($p = 0.799$, 0.092, and 0.124, respectively) between *BRCA 1/2* carriers and non-carriers, although *BRCA 1/2* carriers showed significantly worse contralateral breast cancer-free survival ($p < 0.0001$) than non-carriers.

Conclusion In unselected TNBC patients, we found *BRCA 1/2* mutations in 13.1% of overall patients and 14.5% of patients ≤ 60 years. We suggest that Korean women with TNBC diagnosed at ≤ 60 years should be tested for *BRCA1/2* mutation.

Keywords Triple-negative Breast Neoplasms · Mutation · Breast neoplasm · *BRCA 1/2*

Introduction

Triple-negative breast cancer (TNBC), which is defined by little or lack of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2), accounts for 10–20% of all breast cancer (BC)s in Western countries [1, 2]. *BRCA 1* mutation-related BC has been associated with TNBC, with 60 to 80% of *BRCA1* mutation carriers having TNBC [3].

There is increasing evidence that the prevalence of *BRCA 1/2* mutation among patients diagnosed with TNBC before the age of 60 is more than 10%, irrespective of family history (FHx) of BC and/or ovarian cancer (OC) in Western countries. In Western countries, *BRCA 1/2* genetic testing is recommended in TNBC patients who diagnosed ≤ 60 years [4–7]. TNBC is more frequent in young and pre-menopausal women, and it is known that Asian breast cancer patients are younger than those in Western countries [8, 9]. However, in most Asian countries including Korea, *BRCA 1/2* genetic screening is not recommended in patients with TNBC because of lack of evidence and insurance coverage [10].

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In this study, we determined the prevalence of germline *BRCA 1/2* mutations among unselected Korean patients with TNBC using next-generation DNA sequencing (NGS) and analyzed oncologic outcomes according to *BRCA 1/2* mutation status.

Methods

A retrospective review was conducted to identify breast cancer patients who underwent surgery at Samsung Medical Center (SMC) between July 2008 and January 2016. We conducted *BRCA 1/2* genetic testing by NGS in SMC biobank samples from the unselected TNBC patients.

Data collection

We collected the following variables: genetic data (*BRCA 1/2* genetic test results, age at diagnosis, FHx of BC and/or OC, number of relatives with BC and/or OC within third-degree relatives), clinicopathological data (menopause status, pathologic stage according to 7th edition of American Joint Committee on Cancer classification, histopathology, nuclear grade, lymphovascular invasion, bilateral BC), and personal cancer history of OC. ER and PR expression were measured primarily by immunohistochemistry (IHC). Staining of 1% of cells or more was considered positive for ER and PR [11]. Only membrane staining intensity and pattern were evaluated using the recommendations of the 2013 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) [12]. TNBC was immunohistochemically defined as ER/PR-negative and lacking overexpression of HER-2.

BRCA1/2 mutation analysis

Genomic DNA was extracted from peripheral blood using MG blood genomic DNA extraction SV miniprep (MGmed, South Korea). Full sequencing of all coding exons and all adjacent exon/intron boundaries of *BRCA 1/2* was achieved using the TruSeq custom amplicon *BRCA* panel kit (Illumina, San Diego, CA) according to the manufacture's protocol. A total of 150 amplicons with an average amplicon target length of 211 bp were amplified to create sequencing libraries of the complete *BRCA 1/2* genes in a single tube. 100 ng of genomic DNA was used to amplify the *BRCA 1/2* genes in a single-tube multiplex reaction; this PCR-based library incorporated molecular barcodes and adapter sequences into each amplicon by a second PCR reaction. The final library was normalized to a concentration of 2 nM and prepared for sequencing using Illumina MiSeq with Miseq Reagent Kit v2 (300-cycles) (Illumina, San Diego, CA) according to the manufacturer's instructions to generate paired-end reads. Sequenced reads of each sample (average sequence depth of 1200 ×) were aligned to the reference sequence hg19 using BWA mem. Germline variants identified using GATK Haplotype Caller were annotated with clinical significance from the NCBI ClinVar database. Interpretation of sequence variants was followed the American College of Medical Genetic guidelines [13]. All mutations are described according to the HUGO-approved systematic nomenclature (http://www.hgvs.org/mutnomen/). Reference sequences and GeneBank accession numbers NM_007294.2 and NM_000059.3 were used for *BRCA1* and *BRCA2* DNA numbering, respectively. We performed a validation test to confirm the feasibility of using NGS to detect germline *BRCA 1/2* mutations using previously *BRCA 1/2* mutations identified by the Sanger method according to current Korean genetic screening guidelines in a same cohort.

Statistical analysis

Patient characteristics were compared using independent t-test for continuous variables and Chi square or Fisher's exact test for categorical variables. Kaplan–Meier curves, with corresponding log-rank tests, were constructed for disease-free survival (DFS), overall survival (OS), breast cancer-specific survival (BCSS), and contralateral breast cancer-free survival (CBCFS). Values are reported as mean ± standard deviation (SD) or median with range. All tests were two-sided, and $p < 0.05$ was considered significant. All statistical analyses were done using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R3.4.0 (Vienna, Austria; http://www.R-project.org). This study adhered to the ethical tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of SMC in Seoul, Korea (IRB number: 2017-06-130). The need for informed consent was waived because of the low risk posed by this investigation.

Results

Basic characteristics

Among 11,994 BC patients who underwent surgery at SMC between July 2008 and January 2016, 1628 patients were identified to have TNBC. Of those, 1000 TNBC samples were available from the SMC biobank. One patient was excluded because of inadequate sample, and 999 patients were enrolled. All patients were Korean. We observed 131 *BRCA 1/2* mutation carriers (13.1%) and 132 *BRCA 1/2* pathogenic or likely pathogenic variants in the 999 TNBC patients (Fig. 1). Of the mutation carriers, 73.5% (97 patients) and 26.5% (35 patients) showed mutation in *BRCA1* and *BRCA2*, respectively. One patient

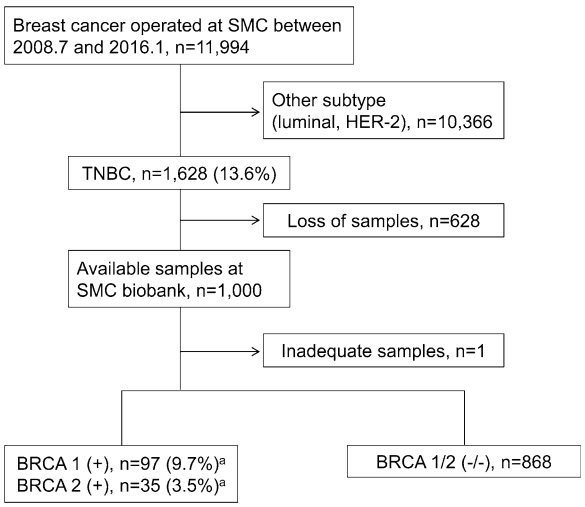

Fig. 1 Schematic diagram of patient selection

had both *BRCA1* and *BRCA2* mutations. *BRCA 1/2* mutation carriers were more likely to have FHx of BC and/or OC (38.9% vs. 8.6%, $p < 0.0001$), bilateral BC (5.3% vs. 1.3%, $p = 0.005$), personal history of OC (3.8% vs. 0.7%, $p = 0.009$), and high nuclear grade (85.5% vs. 73.7%, $p = 0.004$) (Table 1). Histopathology, pathologic stage, types of operation, and adjuvant treatment were not significantly different in those with or without *BRCA 1/2* mutation.

Spectrum of *BRCA 1/2* mutations

We previously examined 103 patients with TNBC from the same cohort by the Sanger method; 50 (48.5%) patients had a *BRCA1/2* mutation (41 *BRCA1* and 9 *BRCA2* mutations). All *BRCA1/2* pathogenic/likely pathogenic variants were identified using NGS. The spectrum of *BRCA1* and *BRCA 2* mutations is summarized in Tables 2 and 3. Overall, 68 distinct pathologic (P) or likely pathogenic (LP) variants (43 *BRCA1* and 25 *BRCA2*) were found in 131 *BRCA 1/2* mutation carriers. We looked at nonsense, frameshift, missense, and splice-defect P or LP variants and found 21, 60, 9, and 7, respectively, in *BRCA1* patients and 19, 14, 0, and 2 in *BRCA2* patients. The frequent P variants in *BRCA1* were c.3627dupA (p.Glu1210Argfs), c.923_924delGC (p.Ser308Lysfs), and c.5339T > C (p.Leu1780Pro) (16 (12.1%), 14 (10.6%), and 8 (8.2%) times, respectively). The most frequent P variant in *BRCA2* was c.7480C > T (p.Arg2494Ter), which was found 6 times (17.1% of *BRCA2* P variants and 4.6% of all P variants).

BRCA 1/2 prevalence according to age

The distribution of age at diagnosis is shown in Table 4 and Fig. 2. The prevalence of *BRCA 1/2* mutation was 13.1% overall, 14.5% in the ≤60 year-old group, and 5.3% in the >60 year-old group. Age at diagnosis ranged from 22 to 90 years, with a median age of 50.3 years. The mean age was significantly younger with *BRCA 1/2* mutation (45.5 years; $p < 0.0001$) and *BRCA1* mutation (43.9 years; $p = 0.003$) relative to *BRCA 1/2* non-carriers (50.3 years). The mean age of *BRCA2* carriers (50.3 years, $p = 1.000$) was not significantly different from that of non-carriers.

Age at diagnosis of breast cancer and family history of breast and/or ovarian cancer

Overall, the prevalence of *BRCA1/2* mutation was 40.5% among 126 (12.6%) patients with familial BC and 9.2% among patients without familial BC (Tables 5, 6). The prevalence of *BRCA 1/2* mutation was 9.8% in the ≤60 year-old group without FHx of BC and/or OC. The difference in mean age between familial and non-familial BC patients among the *BRCA1/2* and *BRCA1/2* mutation non-carriers was not statistically significant ($p = 0.093$ and 0.758, respectively) (Table 7).

Oncologic outcomes

The median follow-up duration was 53.6 months (range, 1-110 months). In the *BRCA1/2* mutation carriers, there were 20 (20.8%) recurrences, 11 (11.5%) distant metastasis, 4 (2.8%) contralateral breast recurrences, and 8 (8.3%) deaths. In the *BRCA1/2* non-carriers, there were 23 (17.6%) recurrences, 12 (9.2%) distant metastasis, 4 (0.5%) contralateral breast recurrence, and 9 (6.9%) deaths. Five-year and 8-year DFS estimates were 81.5% and 66.8% for *BRCA1/2* carriers versus 79.7% and 75.4% for *BRCA1/2* non-carriers ($p = 0.684$ and 0.300, respectively); 91.3% and 84.3% for *BRCA1/2* carriers versus 86.6% and 82.2% for *BRCA1/2* non-carriers ($p = 0.185$ and 0.729, respectively); and 94.7% and 78.3% for *BRCA1/2* carriers versus 99.1% and 99.1% for *BRCA1/2* non-carriers ($p = 0.114$ and 0.016, respectively). There was no significant difference in DFS, OS, and BCSS ($p = 0.799$, 0.092, and 0.124, respectively) between *BRCA1/2* carriers and non-carriers, although *BRCA1/2* carriers showed significantly worse CBCFS than non-carriers ($p < 0.0001$) (Fig. 3).

Discussion

In this study, we determined that the prevalence of *BRCA1/2* mutations was 131 among 999 (13.1%) Korean unselected TNBC patients, with 14.5% of *BRCA1/2* mutations

Table 1 Patients characteristics

	BRCA1, n (%)	*BRCA2, n* (%)	Total, *n* (%)	non-*BRCA 1/2*, *n* (%)	*p* value
Number, %	n = 97[a]	n = 35[a]	n = 131	n = 868	
Mean age, ±SD	43.9 (± 10.2)	50.3 (± 11.3)	45.5 (± 10.8)	50.3 (± 11.0)	< 0.0001
Age					0.0001
≤40	36 (37.1)	5 (14.3)	41 (31.3)	171 (19.7)	
41–60	58 (59.8)	25 (71.4)	82 (62.6)	553 (63.7)	
≥61	3 (3.1)	5 (14.3)	8 (6.1)	144 (16.6)	
Menopausal status					0.0001
Premenopause	28 (29.2)	18 (52.9)	46 (35.1)	463 (53.3)	
Postmenopause	68 (70.8)	16 (47.1)	85 (64.9)	405 (46.7)	
FHx of BC and/or OC					< 0.0001
Yes	42 (43.8)	9 (26.5)	51 (38.9)	75 (8.6)	
No	54 (56.2)	25 (73.5)	80 (61.1)	793 (91.4)	
Bilaterality					0.004
Bilateral	6 (6.2)	1 (2.9)	7 (5.3)	11 (1.3)	
Unilateral	90 (93.8)	33 (97.1)	124 (94.7)	857 (98.7)	
LVI					0.254
Yes	28 (29.2)	4 (11.8)	32 (24.4)	258 (29.7)	
No	68 (70.8)	30 (88.2)	99 (75.6)	610 (70.3)	
Histopathology					0.178
IDC	84 (87.5)	30 (88.2)	115 (87.8)	759 (87.4)	
ILC	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.8)	
DCIS	0 (0.0)	1 (2.9)	1 (0.8)	31 (3.6)	
Mixed or others	12 (12.5)	3 (8.8)	15 (11.5)	71 (8.2)	
Nuclear grade					0.004
Low	0 (0.0)	1 (2.9)	1 (0.8)	12 (1.4)	
Intermediate	7 (7.3)	6 (17.6)	13 (9.9)	164 (18.9)	
High	85 (88.5)	26 (76.5)	112 (85.5)	640 (73.7)	
Unknown	4 (4.2)	1 (2.9)	5 (3.8)	52 (6.0)	
Pathologic stage					0.385
Stage 0	5 (5.2)	3 (8.8)	8 (6.1)	88 (10.1)	
Stage I	44 (45.8)	18 (52.9)	62 (47.3)	363 (41.8)	
Stage II	41 (42.7)	13 (38.2)	55 (42.0)	373 (43.0)	
Stage III	6 (6.2)	0 (0.0)	6 (4.6)	36 (4.1)	
Stage IV	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.6)	
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	
Personal history of OC					0.009
Yes	5 (5.2)	0 (0.0)	5 (3.8)	6 (0.7)	
No	91 (94.8)	34 (100.0)	126 (96.2)	862 (99.3)	
Any recurrence					0.904
Yes	20 (20.8)	3 (8.8)	23 (17.6)	160 (18.4))	
No	76 (79.2)	31 (91.2)	108 (82.4)	708 (81.6)	
Distant meta					0.317
Yes	11 (11.5)	1 (2.9)	12 (9.2)	110 (12.7)	
No	85 (88.5)	33 (97.1)	119 (90.8)	758 (87.3)	
Expire					0.108
Yes	8 (8.3)	1 (2.9)	9 (6.9)	105 (12.1)	
No	88 (91.7)	33 (97.1)	122 (93.1)	763 (87.9)	

BC breast cancer, *OC* ovarian cancer

[a]One patient has both *BRCA 1* and *BRCA 2* mutation

Table 2 The spectrum of *BRCA 1* mutations ($n=97$)

Exon/intron	HGVS nomenclature-cDNA level	HGVS nomenclature- Protein change	Effect	Number
2	c.38_39delATinsGGG	p.Asn13fs	Frameshift	1
3	c.131G > T	p.Cys44Phe	Missense	1
6	c.277_279delTTTinsCC	p.Phe93fs	Frameshift	1
7	c.390C > A	p.Tyr130Ter	Nonsense	6
IVS8	c.547 + 1G > A		Abnormal splicing	1
10	c.1292T > G	p.Leu431Ter	Nonsense	1
10	c.1511dupG	p.Lys505Terfs	Nonsense	1
10	c.4057_4061del	p.Glu1353Terfs	Nonsense	1
11	c.923_924delGC	p.Ser308Lysfs	Frameshift	14
11	c.928C > T	p.Gln310Ter	Nonsense	1
11	c.1292T > G	p.Leu431Ter	Nonsense	1
11	c.1511dupG	p.Lys505Terfs	Frameshift	1
11	c.1716delA	p.Glu572Aspfs	Frameshift	1
11	c.1823delA	p.Lys608Argfs	Frameshift	1
11	c.1961delA	p.Lys654Serfs	Frameshift	1
11	c.2433delC	p.Lys812Argfs	Frameshift	1
11	c.2630delA	p.Asn877Metfs	Frameshift	1
11	c.2856_2857delTT	p.Phe952Leufs	Frameshift	1
11	c.2864C > G	p.Ser955Ter	Nonsense	1
11	c.3266T > A	p.Leu1089Ter	Nonsense	1
11	c.3277delG	p.Asp1093Metfs	Frameshift	1
11	c.3296delC	p.Pro1099Leufs	Frameshift	2
11	c.3442delG	p.Glu1148Argfs	Frameshift	2
11	c.3627dupA	p.Glu1210Argfs	Frameshift	16
11	c.3770_3771delAG	p.Glu1257Glyfs	Frameshift	1
11	c.3954dupT	p.Gly1319Trpfs	Frameshift	2
11	c.3991C > T	p.Gln1331Ter	Nonsense	1
11	c.4041_4042delAG	p.Gly1348Asnfs	Frameshift	1
12	c.4127_4128delCA	p.Thr1376fs	Frameshift	1
IVS12	c.4185 + 1G > T		Abnormal splicing	1
13	c.4253delT	p.Leu1418fs	Frameshift	1
13	c.4335_4338dupAGAA	p.Gln1447fs	Frameshift	1
16	c.4981G > T	p.Glu1661fs	Nonsense	1
IVS17	c.5074 + 1G > T		Abnormal splicing	1
18	c.5102_5103delTG	p.Leu1701Glnfs	Frameshift	1
IVS18	c.5152 + 1G > C		Abnormal splicing	1
IVS19	c.5193 + 1G > C		Abnormal splicing	1
IVS21	c.5333-2A > T		Abnormal splicing	1
22	c.5339T > C	p.Leu1780Pro	Missense	8
23	c.5445G > A	p.Trp1815Ter	Nonsense	6
IVS23	c.5467 + 1G > A		Abnormal splicing	1
24	c.5496_5506delinsA	p.Val1833Serfs	Frameshift	6
24	c.5483delG	p.Cys1828Leufs	Frameshift	2

prevalence diagnosed with TNBC at an age ≤ 60 years. TNBC patients without FHx, the prevalence of *BRCA 1/2* mutations was 9.8% at an age ≤ 60 years. OS, BCSS, and DFS were not different between *BRCA1/2* carriers and non-carriers, although CBCFS was significantly worse in *BRCA1/2* carriers than non-carriers. NCCN guidelines recommend the genetic screening that the probability of *BRCA 1/2* mutation is more than 10.0%, and thus our data provide the evidence for *BRCA1/2* genetic testing in Korean women diagnosed with TNBC at ≤ 60 years.

Table 3 The spectrum of *BRCA 2* mutations ($n=35$)

Exon/intron	HGVS nomenclature-cDNA level	HGVS nomenclature- Protein change	Effect	Number
8	c.658_659delGT	p.Val220Ilefs	Frameshift	1
9	c.771_775delTCAAA	p.Asn257Lysfs	Frameshift	1
10	c.1321_1324delACTT	p.Thr441Glnfs	Frameshift	1
10	c.1399A > T	p.Lys467Ter	Nonsense	4
11	c.2548C > T	p.Gln850Ter	Nonsense	1
11	c.2798_2799delCA	p.Thr933fs	Frameshift	1
11	c.2983G > T	p.Gly995Ter	Nonsense	1
11	c.3018delA	p.Gly1007Valfs	Frameshift	1
11	c.3096_3110delAGATATTGAAGAACAinsT	p.Lys1032Asnfs	Frameshift	1
11	c.4037_4038delCT	p.Thr1346Serfs	Frameshift	1
11	c.4471_4474del	p.Leu1491Lysfs*12	Nonsense	1
11	c.5576_5579delTTAA	p.Ile1859Lysfs	Frameshift	1
11	c.6547_6550delGAAC	p.Glu2183fs	Frameshift	1
11	c.6553delG	p.Ala2185Leufs	Frameshift	1
11	c.6724_6725delGA	p.Asp2242Phefs	Frameshift	3
IVS13	c.7008-1G > T		Abnormal splicing	1
14	c.7258G > T	p.Glu2420Ter	Nonsense	1
15	c.7480C > T	p.Arg2494Ter	Nonsense	6
15	c.7538delC	p.Ala2513Glufs	Frameshift	1
19	c.8363G > A	p.Trp2788Ter	Nonsense	1
IVS19	c.8488-1G > A		Abnormal splicing	1
20	c.8572C > T	p.Gln2858Ter	Nonsense	1
23	c.8969G > A	p.Trp2990Ter	Nonsense	1
23	c.9105T > G	p.Tyr3035Ter	Nonsense	1
23	c.9076C > T	p.Gln3026Ter	Nonsense	1

Table 4 *BRCA 1/2* mutation rates across age groups

Age group	*BRCA 1* mutation, n	*BRCA 2* mutation, n	*BRCA 1/2* mutation, n	Non-*BRCA 1/2* mutation, n	Total, n	*BRCA 1/2* mutation rate, %	Cumulative *BRCA 1/2* mutation rate, %
20–30	5	1	6	18	24	25.0	25.0
31–35	14	2	16	68	84	19.0	20.1
36–40	17	2	19	85	104	18.3	19.3
41–45	25[a]	7[a]	31	117	148	20.9	20.0
46–50	14	8	22	152	174	12.6	17.6
51–55	10	8	18	166	184	9.8	15.6
56–60	9	2	11	118	129	8.5	14.5
60+	3	5	8	144	152	5.3	13.1
Total	97	35	131	868	999	13.1	13.1

[a]One patient has both *BRCA 1* and *BRCA 2* mutation

There have been numerous studies on the prevalence of *BRCA1/2* mutation among unselected TNBC patients from Western countries [5]. However, only a few studies have reported on Asian patients. Kwong et al. [10] reported the comprehensive spectrum of *BRCA1/2* mutation from 47 Asian countries and population (11 participating Asian countries; Bangladesh, Mainland China, Hong Kong, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Thailand, and Vietnam/ from ethnic Asians residing in Canada and the USA/ from a literature review including other Asian countries). They reported that the prevalence of *BRCA1/2* mutation in a high-risk group, not in unselected

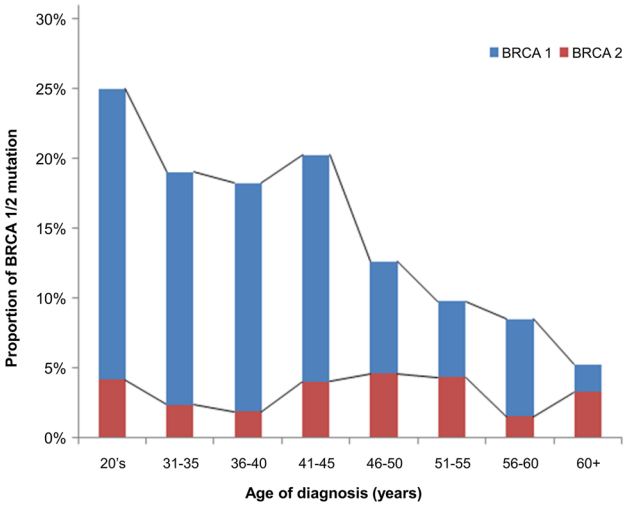

Fig. 2 Distribution of age of diagnosis for patients with BRCA1/2 mutation

TNBC patients, ranged from 17.4% to 25.5% [10]. Few studies have reported the prevalence of *BRCA1/2* mutation in unselected TNBC in Asia. Zhang et al. [14] reported an incidence of 9.4% for *BRCA1/2* mutation (71 in *BRCA1* and 22 in *BRCA2*) among 990 patients with unselected TNBC in China. Zhong et al. [15] reported a prevalence of 20.6% for germline *BRCA1/2* mutation (14 *BRCA1* and 11 *BRCA2* mutations) among 64 patients with unselected TNBC in China. In Korea, Jung et al. [16] reported that the prevalence of *BRCA 1/2* mutation in a high-risk (not unselected) group of 93 TNBC patients was 26.9%. To the best of our knowledge, this study is the first report on the prevalence of *BRCA1/2* mutation among unselected TNBC patients in Korea, and the prevalence of *BRCA1/2* mutation among unselected TNBC patients in Korea was similar to that in Western countries.

Using current Korean breast cancer genetic screening guidelines, which include BC patients less than 40 years, FHx of BC and/or OC, male BC patients, and personal history of OC but not TNBC, it would be highly possible to underestimate the number of *BRCA1/2* mutation carriers [17]. The age distribution of patients with BC in Korea

Table 5 *BRCA 1/2* mutation rates among patients with family history of breast and/or ovarian cancer across age groups (n = 126)

Age group	*BRCA 1* mutation, n	*BRCA 2* mutation, n	*BRCA 1/2* mutation, n	Non-*BRCA 1/2* mutation, n	Total, n	*BRCA 1/2* mutation rate, %	Cumulative *BRCA 1/2* mutation rate, %
20–30	2	0	2	0	2	100.0	100.0
31–35	9	0	9	6	15	60.0	64.7
36–40	4	1	5	8	13	38.5	53.3
41–45	11	1	12	9	21	57.1	54.9
46–50	8	3	11	13	24	45.8	52.0
51–55	4	4	8	19	27	29.6	46.1
56–60	4	0	4	7	11	36.4	45.1
60+	0	0	0	13	13	0	40.5
Total	42	9	51	75	126	40.5	

Table 6 *BRCA 1/2* mutation rates among patients without family history of breast and/or ovarian cancer across age groups

Age group	*BRCA 1* mutation, n	*BRCA 2* mutation, n	*BRCA 1/2* mutation, n	Non-*BRCA 1/2* mutation, n	Total, n	*BRCA 1/2* mutation rate, %	Cumulative *BRCA 1/2* mutation rate, %
20–30	3	1	4	18	22	18.2	18.2
31–35	5	2	7	62	69	10.1	12.1
36–40	13	1	14	77	91	15.4	13.7
41–45	14[a]	6 [a]	19	108	127	15.0	14.2
46–50	6	5	11	139	150	7.3	12.0
51–55	6	4	10	147	157	6.4	10.6
56–60	5	2	7	111	118	5.9	9.8
60+	3	5	8	131	139	5.8	9.2
Total	54	25	80	793	873	9.2	

[a]One patient has both *BRCA 1* and *BRCA 2* mutation

Table 7 The relation between age and family history

	FHx. of breast and/or ovarian cancer (+)		FHx. of breast and/or ovarian cancer (−)		*p*-value
	Number (%)	Mean age (±SD)	Number (%)	Mean age (±SD)	
	n = 126 (12.6)	47.8 (±10.8)	*n* = 873 (87.4)	49.9 (±11.1)	0.039
BRCA 1/2 (+)	51 (40.5)	44.7 (±8.5)	80 (9.2)	46.7 (±12.0)	0.093
BRCA 1	42 (33.3)	42.7 (±8.8)	55[a] (6.3)	44.8 (±11.2)	
BRCA 2	9 (7.1)	48.3 (±5.2)	26[a] (3.0)	51.0 (±12.8)	
BRCA 1/2 (-)	75 (59.5)	50.6 (±10.8)	793 (90.8)	50.2 (±11.0)	0.758

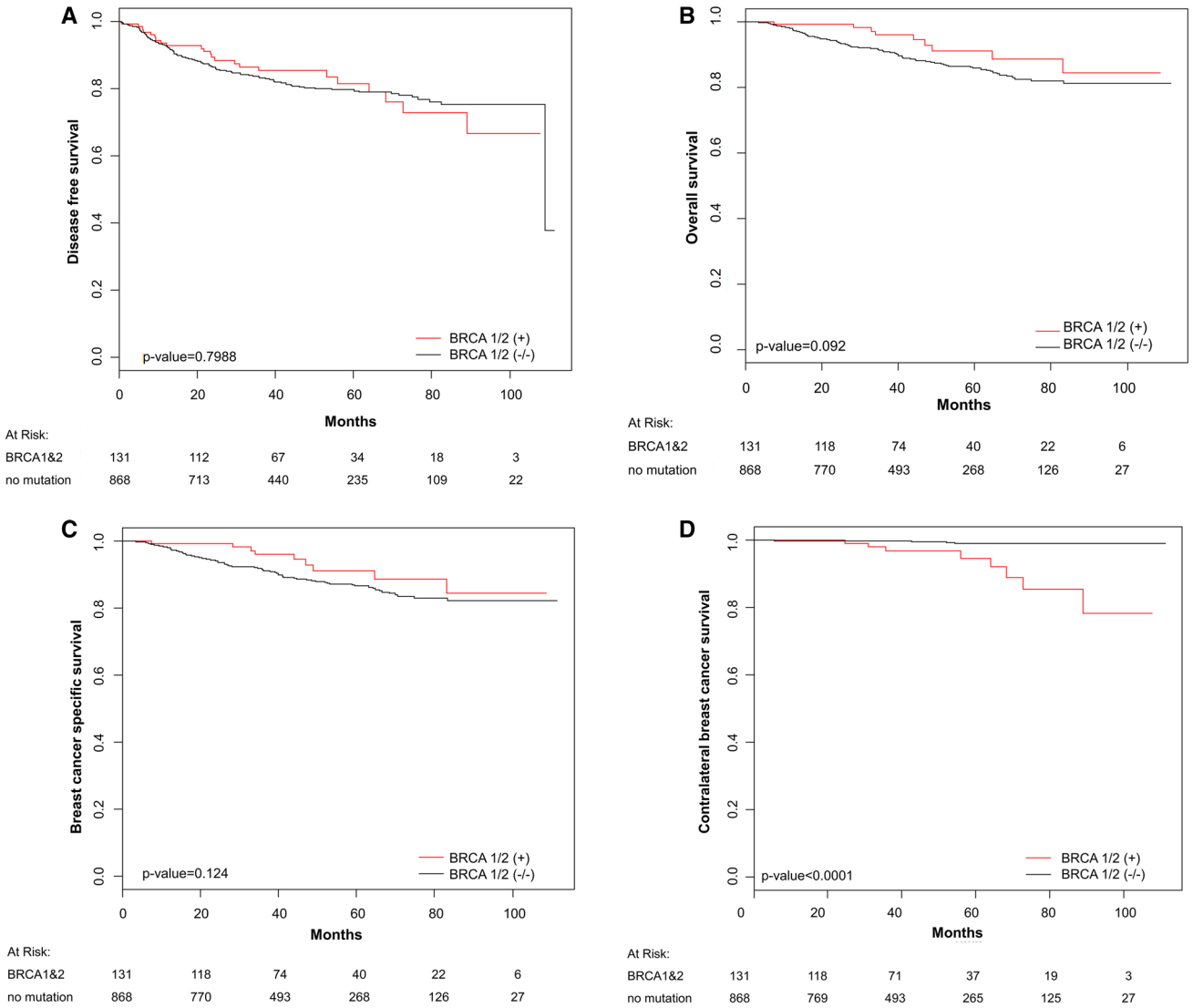

Fig. 3 Kaplan–Meier curves with corresponding log-rank tests for disease-free survival (DFS) (**a**), overall survival (OS) (**b**), breast cancer-specific survival (BCSS) (**c**), and contralateral breast cancer survival (CBCS) (**d**)

is much younger than that in the US; the median age of BC in Korea is 50 years versus 62 years in the US, and the peak age group in Korea is 40 s (35.0% of cases), followed by 50 s, 60 s, 30 s, and 70 s. The peak age group in the US is 55–64 years (25.9% of cases), followed by 65–74, 45–54, 75–84, > 84, and 20–34 years [8, 18]. Because of the age distribution, a higher proportion of patients with TNBC are expected in Korea [19, 20]. Using data from the

Korean Breast Cancer Society Registry, we observed that TBNC tended to occur more often in the younger age group than in the older group among patients less than 50 years (TNBC; 29.8% vs. 24.4% vs. 16.7% in the 20–29, 30–39, and 40–49 years, respectively) [21]. Consequently, there is a high possibility of underestimating the risk of BRCA1/2 mutation in patients with TNBC using current Korean breast cancer genetic screening guidelines. We previously examined 103 patients with TNBC by the Sanger method in the same cohort according to current Korean breast cancer genetic screening guidelines and observed 81 (61.8%) missed *BRCA1/2* mutation carriers. Furthermore, among 719 patients with TNBC diagnosed at ≤ 60 years who were not tested with the *BRCA1/2* genetic test, we found 71 (9.9%) with *BRCA1/2* mutation. Of those, 54 (76.1%) did not have a FHx of BC and/or OC. These results show that we would have missed a relatively large set of *BRCA1/2*-related BC patients if we had followed the current Korean breast cancer genetic screening guidelines. In Korea, 21,484 patients were newly diagnosed with breast cancer in 2014; of those, approximately 65% were 40–59 years, and around 15% were TNBC [22]. We assumed 2,094 patients were newly diagnosed with TNBC. In this study, we observed 87.4% did not have FHx of BC and/or OC, and 14.8% were *BRCA 1/2* mutation among 41–60 years, and thus we predict that about 270 *BRCA 1/2* carriers with TNBC are missed annually. This underestimation could have serious ethical implications for patients as well as their families.

There are several important reasons for appropriate *BRCA 1/2* mutation screening in TNBC patients. First, risk-reducing bilateral salpingo-oophorectomy could decrease the risk of breast cancer, mortality, and *BRCA*-related gynecologic cancer in *BRCA 1/2* mutation patients [23, 24]. Second, there is increasing evidence that *BRCA 1/2*-related advanced or metastatic BC shows better response to DNA-damaging treatment regimens, including PARP inhibitor [25–28]. *BRCA1/2* mutation status is considered as a valuable biomarker, especially in patients with TNBC [29]. Consequently, patients who know their *BRCA1/2* mutation status could undergo appropriate target therapy. Third, the families of *BRCA 1/2* carriers could receive appropriate genetic counselling and surveillance.

The prognostic role of *BRCA1/2* mutation status in breast cancer patients is still unclear. Recently, a comprehensive systematic review and meta-analysis of 60 studies demonstrated that *BRCA1/2* mutation carriers have worse OS (Hazard ratio; HR 1.19, 95%, confidence interval; CI 1.04–1.35, $p = 0.009$) and BCSS (HR 1.22, 95% CI 1.04–1.44, $p = 0.02$) than non-carriers [30]. Recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) of *BRCA1/2* mutation carriers were not significantly different from those of non-carriers [30]. Regarding the prognosis of *BRCA1/2* mutation status in TNBC patients, some studies have reported that *BRCA1/2* mutation carriers have better OS than non-carriers (HR 0.49, 95% CI 0.26–0.92; $p = 0.02$), and that DFS is not statistically different between *BRCA1/2* carriers and non-carriers (HR 0.60, CI 0.30–1.19; $p = 0.14$) [31, 32]. However, the median follow-up duration was relatively short, less than 4 years in both studies. Of 558 patients with TNBC in the Prospective Outcomes in Sporadic versus Hereditary breast cancer (POSH) study, in which the median follow-up duration was 8.2 years, *BRCA1/2* mutation carriers had better OS than non-carriers at 2 years (95% versus 91%; HR 0.59, 95% CI 0.35–0.99; $p = 0.047$) but not 5 years (81% vs 74%; HR 1.13, 95% CI 0.70–1.84; $p = 0.62$) or 10 years (72% versus 69%; HR 2.12, 95% CI 0.82–5.49; $p = 0.12$) [33]. Our study, in which the median follow-up duration was 53.6 months, similarly showed that DFS, OS, and BCSS were not significantly different between *BRCA1/2* mutation carriers and non-carriers. However, CBCFS was significantly worse in *BRCA1/2* mutation carriers than in non-carriers. Eighty-one of 131 (61.8%) *BRCA1/2* carriers had not been previously noted as carriers and, consequently, did not receive appropriate genetic counselling or risk-reducing contralateral mastectomy or bilateral salpingo-oophorectomy. These cases of mismanagement might have caused worse CBCFS in *BRCA1/2* mutation carriers.

This study had a few limitations. This study was performed by retrospective review of clinical information, and there was a possibility of incomplete information for family history and recall bias. Although we identified all P/LP variants previously identified by the Sanger method, there is the possibility of loss of P variants by inherent weakness of the amplicon method. Despite these limitations, the results of this study are valuable, because this is the first report on the prevalence of *BRCA1/2* mutations among unselected TNBC in a relatively large and homogenous Korean population. In the future, *BRCA1/2* mutation prediction models should be developed to consider age, family history, and other risk factors for hereditary breast and/or ovarian cancer syndrome.

In conclusion, we demonstrated that the prevalence of *BRCA 1/2* mutation in unselected TNBC at an age ≤ 60 years is 13.1%. Our data provide the evidence for BRCA1/2 genetic testing in Korean women diagnosed with TNBC at ≤ 60 years.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This study adhered to the ethical tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of SMC in Seoul, Korea (IRB number: 2017-06-130).

Informed consent The need for informed consent was waived because of the low risk posed by this investigation.

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