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Original

BRCA1 / 2 Mutation Frequency is HIGH in Japanese Triple-Negative Breast Cancer Patients

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Abstract: Germline mutations of BRCA1 / 2 genes cause hereditary breast and / or ovarian cancer. However, whether guidelines like those of the National Comprehensive Cancer Network (NCCN) can suitably predict the likelihood of BRCA1 / 2 mutations in the Japanese population is unclear. Methods BRCA1 / 2 gene mutation frequencies were investigated in relation to parameters such as age, family history (FH), and breast cancer subtype using data collected from 922 Japanese breast cancer patients who underwent surgery between September 2010 and June 2013. BRCA1 / 2 mutations were present in 15 of 57 (26.3%) tested patients. The frequency of the mutations was not significantly related to age. Among the 180 patients who reported an FH of breast cancer, 11 of the 37 who were tested (29.7%) were positive for BRCA1 / 2 mutations. Of those with an FH of ovarian cancer (n = 34), seven of 12 patients tested (58.3%) were carriers of BRCA1 / 2 ($P = 0.013$). Six of these seven carriers were triple-negative breast cancer (TNBC) patients. In all, there were 97 TNBC patients, and the presence of the BRCA1 / 2 mutation in this subgroup was significantly greater than in non-TNBC patients, with 12 of 17 TNBC patients (70.5%) testing positive ($P = 0.03$). There were 59 TNBC patients <60 years of age, and of the 16 (27.1%) who underwent BRCA1 / 2 genetic testing, 11 (68.8%) were found to have mutations in BRCA1 / 2. Among the TNBC patients, 29 also reported an FH of breast or ovarian cancer; of these, nine of the 13 tested (69.2%) were positive for a BRCA1 / 2 mutation. The data demonstrate that BRCA1 / 2 mutations are observed more frequently in TNBC patients, especially those <60 years of age or in combination with an FH of breast and / or ovarian cancer, suggesting that some of the NCCN guidelines can adequately predict BRCA1 / 2 carriers in the Japanese population.

Key words: BRCA1, Japanese, triple negative, breast cancer

Introduction

BRCA1 (MIM 113705) and BRCA2 (MIM 600185) are autosomal dominant tumor suppressor genes that mediate the DNA damage response to double-stranded DNA breaks by homologous

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recombination. Germline mutations of these two genes are associated with the early onset and / or familial forms of breast cancer. According to previous reports, BRCA1 / 2-related breast cancer accounts for approximately 5%～10% of all breast cancers diagnosed[1]. It is estimated that, by 70 years of age, the average cumulative risk of breast cancer in carriers of BRCA1 and BRCA2 mutations is in the range 60%～70% and 45%～55%, respectively[2–5]. Notably, triple negative breast cancer (TNBC) is more common in individuals with the BRCA1 mutation than in those without this mutation. TNBC is defined as an absence of staining for estrogen receptor, progesterone receptor, and Her2 / neu. TNBC accounts for approximately 15% of all breast cancers, and 70% of individuals with the BRCA1 mutation have TNBC[2, 6]. In ovarian cancer, the risk of TNBC has been estimated to be 40% and 20% for carriers of BRCA1 and BRCA2 mutations, respectively[3, 4]. Furthermore, carriers of BRCA1 and BRCA2 mutations are at an increased risk of developing fallopian tube, colon, prostate and pancreatic cancers, as well as melanoma[2, 4, 5]. It is well known that Ashkenazi Jews have a high frequency of BRCA1 / 2 mutations[5]. Recently, several studies have reported that Asian populations have a similarly high frequency of BRCA1 / 2 mutations[7–9]. In Japan, the actual frequency of BRCA1 / 2 mutations in the general population is not clear. Moreover, there is a tendency for earlier onset of disease and a higher frequency of hormone receptor-positive tumors in Japanese breast cancer patients compared with Caucasian populations[10–12]. Furthermore, the National Comprehensive Cancer Network (NCCN) has published guidelines about risk reduction after genetic assessment of breast and ovarian cancer[13]. However, because the characteristics of breast cancer in Japanese BRCA1 / 2 carriers may differ from those of Caucasian women, it is not clear whether these guidelines are suitable for the Japanese population. Therefore, the purpose of the present study was to determine the occurrence of BRCA1 / 2 mutations in Japanese breast cancer patients, and its association with factors such as age, family history (FH), and cancer subtype, and to consider the eligibility criteria for BRCA1 / 2 genetic testing in comparison with the NCCN guidelines. Herein we report the findings of an investigation regarding the outcomes of BRCA1 / 2 genetic testing and mutations in Japanese breast cancer patients receiving treatment at Showa University Hospital.

Patients and methods

Nine hundred and twenty-two Japanese breast cancer patients who underwent surgery at Showa University Hospital between September 2010 and June 2013 were included in the study. Detailed patient information was collected from medical records and included personal history, FH, breast cancer clinicopathological data, and the BRCA1 and BRCA2 mutation status. Genetic counseling was recommended to patients according to NCCN guidelines. Specifically, genetic counseling was recommended to patients with: (1) an FH of breast and / or ovarian cancers; (2) early onset, especially ＜40 years of age; (3) TNBC at ＜60 years of age; and (4) bilateral breast cancer. Patients were determined to have a positive FH when a first-, second-, or third-degree relative had had breast or ovarian cancer. Doctors and certified genetic counselors administered a structured questionnaire to women who gave informed consent to receive genetic

counseling as part of this study.

Blood samples obtained from patients were analyzed for the presence of BRCA1 / 2 mutations at Falco Biosystems (Kyoto, Japan) using a direct sequencing method. If mutations were not detected using this method, samples were subjected to multiplex ligation-dependent probe amplification (MLPA) to check for BRCA1 / 2 genetic rearrangements.

Statistical analyses of BRCA1 / 2 genetic mutations were performed using SPSS version 19 (SPSS, IBM, Chicago, IL, USA). Pearson's χ^2 test and Fisher's exact test were used to evaluate associations between patient characteristics and genetic mutations. All *P*-values are two-sided and significance was set at $P < 0.05$.

Results

Clinicopathological characteristics of the Japanese breast cancer patient cohort

The characteristics of all patients who underwent surgery for breast cancer at Showa University Hospital are given in Table 1. Briefly, 922 patients with a median age of 52.2 years (range

Table 1. Characteristics of the patient cohort

No. patients	922
Sex	
Female	919
Male	3
Age (years)	
Range	22–97
Median	52.2
Tumor size	
DCIS	159
≤ 2 cm	455
>2 cm, ≤ 5 cm–>2 cm, ≤ 5 cm	176
>5 cm	33
Unknown	99
Lymph nodes	
Negative	660
Positive	205
Unknown	57
Estrogen receptor	
Negative	159
Positive	711
Unknown	52
Progesterone receptor	
Negative	295
Positive	574
Unknown	53
Her2	
Negative	629
Positive	146
2+	93
Unknown	8
Bilateral breast cancer	
Family history of :	
Breast cancer	180
Ovarian cancer	34

Data show the number of patients in each group.

DCIS, ductal carcinoma in situ ; Her2, epidermal growth factor receptor 2.

22～97 years) were recruited to the study. Four hundred and two patients (43.6%) were < 50 years of age.

BRCA1/2 mutation frequency according to age and FH in Japanese breast cancer patients

The number of patients who underwent genetic testing for BRCA1/2 mutations and the results of these tests are given in Table 2. One hundred and sixteen (12.6%) patients received genetic counseling and, of these, 57 (6.2%) agreed to a BRCA1/2 genetic test. Testing revealed that 15 of those patients (26.3%) harbored BRCA1/2 germline mutations. BRCA1 mutations were detected in 11 patients, whereas BRCA2 mutations were detected in four. Of the 11 patients with a BRCA1 mutation, two rearrangement mutations were detected. There was a tendency for a greater number of younger patients to receive genetic counseling and to agree to BRCA1/2 genetic testing. Specifically, counseling rates were 25.4% and 33.3% for patients <45 and <40 years of age, respectively. According to the NCCN guidelines, patient age <50 years is one of the criteria for genetic counseling; thus, according to the NCCN guidelines, 554 patients in our cohort (60.1%) were eligible for genetic counseling. When the age criterion was reduced from <50 to <40 years old, 313 patients (34%) were eligible for counseling. Of these, 87 (27.8%) received genetic counseling and 45 (14.3%) underwent genetic testing, of whom 12 (26.6%) were positive for the BRCA1/2 genetic mutation. There was no significant difference in BRCA1/2 mutation frequencies according to age. Indeed, after genetic testing of patients < 50 years of age, 13 of 40 (23.5%) were found to be positive for BRCA1/2 mutations, which does not differ significantly from the rate in patients >50 years of age (2/17 [11.8%]; $P = 0.18$). In the case of patients <40 years of age, seven of the 22 (31.8%) who underwent testing were positive for BRCA1/2 mutations. This rate was not significantly different from the rate in patients >40 years of age (8/35 [22.9%]; $P = 0.66$).

Similarly, an FH of breast cancer in our patient cohort did not significantly increase the risk of BRCA1/2 mutations compared with no FH of breast and/or ovarian cancer (11/37 vs 3/16, respectively; $P=0.51$). Of the 180 breast cancer patients with an FH of breast cancer, 71 (39.4%) received genetic counseling, 37 (20.6%) underwent BRCA1/2 genetic testing, and 11 of the 37 (29.7%) were found to be carriers. Thirty-four breast cancer patients also reported an FH of ovarian cancer. In this patient subset, 14 (41.2%) received genetic counseling, 12 (35.3%) underwent BRCA1/2 genetic testing, and seven (58.3%) were found to be BRCA1/2 positive, suggesting that there is a significantly higher rate of mutations in patients with an FH of ovarian cancer compared with all patients reporting an FH of cancer in general (7/12 vs 12/41, respectively; $P = 0.013$). The number of patients with an FH of both breast and ovarian cancer was small (12/922), but the rate of BRCA1/2 mutations in this group was very high. Indeed, of the eight patients with an FH of both breast and ovarian cancer who underwent genetic testing, six (75%) were found to be positive for BRCA1/2 mutations.

BRCA1/2 mutation frequency according to age and FH in Japanese TNBC patients

From a biomarker point of view, TNBC accounted for 97 cases (10.5%), with a mean patient

Table 2. BRCA1 / 2 status in Japanese breast cancer patients according to different criteria

	n	Genetic counseling	Genetic testing	BRCA1 / 2 mutation	BRCA1 mutation	BRCA2 mutation	P-value
Age (years)							
All	922	116	57	15	11	4	
≤ 50	402	86	40	13	10	3	
≤ 45	264	67	35	13	10	3	
≤ 40	129	43	22	7	6	1	
≤ 35	49	25	13	1	0	1	
Family history of :							
Breast and ovarian cancer	720	41	16	3	3	0	0.51
Breast or ovarian cancer	202	75	41	12	8	4	
Breast cancer	180	71	37	11	8	3	
Ovarian cancer	34	14	12	7	5	2	
Breast and ovarian cancer	12	9	8	6	5	1	
Biomarker							
Non-TN	825	91	40	3	1	2	0.03
TN		97	25	17	12	10	2
TN (≤ 60 years)	59	21	16	11	10	1	
TN (≤ 50 years)	43	20	15	10	9	1	
TN with a family history of :							
Breast or ovarian cancer	29	18	13	9	7	2	
Breast cancer	20	12	7	3	3	0	
Ovarian cancer	4	1	1	1	0	1	
Breast and ovarian cancer	5	5	5	5	4	1	

Data show the number of patients in each group.
TN, triple negative.

age of 54.9 years. The average age of TNBC patients who received genetic counseling was 43 years, whereas that of TNBC patients who underwent genetic testing was 39.2 years. Of the 17 (17.5%) TNBC patients who underwent BRCA1 / 2 genetic testing, mutations were detected in 12 (70.6%), which was significantly ($P = 0.03$) higher than the detection rate in non-TNBC patients. Almost all patients who received genetic testing were <60 years of age (16 / 17 ; 94.1%). There were 59 TNBC patients < 60 years of age, and they exhibited high BRCA1 / 2 mutagenesis rates. Among the 16 of 59 patients (27.1%) who underwent BRCA1 / 2 genetic testing, 11 (68.8%) were found to have mutations. Thus, even though not all patients underwent genetic testing, the mutation rate is likely to be at least 18.6% (11 / 59) in TNBC patients < 60 years of age. Forty-three TNBC patients were < 50 years old, and 15 (34.9%) of this patient subset underwent BRCA1 / 2 genetic testing, with 10 (66.7%) being found to be positive for BRCA1/2 genetic mutations. The BRCA1 / 2 mutation rate was also examined in TNBC patients with an FH of breast or ovarian cancer (n=29). This subset of patients was found to have an even higher mutagenesis rate than patients without an FH of breast or ovarian cancer. Indeed, of the 29

patients with a positive FH, 13 (44.8%) underwent BRCA1/2 genetic testing and nine (69.2%) were found to be positive. In particular, TNBC patients with an FH of ovarian cancer had a very high mutagenesis rate. Six of the nine patients who had an FH of ovarian cancer (66.6%) underwent genetic testing and all six were found to be positive for BRCA1/2 mutations.

Discussion

In the present study, BRCA1/2 mutations were most frequently observed in TNBC patients, especially those < 60 years of age and with an FH of breast or ovarian cancer.

In general, genetic testing is recommended when the mutation rate is estimated to be > 10%. Some reports have estimated that the rate of BRCA1/2 mutations across all TNBC is 10%～20%[14–16]. According to NCCN guidelines, this is the borderline predicted risk rate recommended for TNBC patients to undergo BRCA1/2 genetic testing.

Two of the parameters used to determine eligibility for BRCA1/2 genetic testing are FH and age. The NCCN guidelines for familial breast cancer recommend that breast cancer patients in the following categories undergo the BRCA1/2 genetic test: (1) patients with early age onset breast cancer, especially < 45 years of age; (2) breast cancer patients < 50 years of age who have more than one close blood relative (i.e. first-, second-, and third-degree relatives; the same applies hereafter) with breast cancer; (3) breast cancer patients who have more than one close blood relative with epithelial ovarian cancer, or more than two close relatives with breast cancer and/or pancreatic cancer; (4) multiple primary breast cancers; (5) a combination of breast cancer with a BRCA1/2-related cancer; and (6) male breast cancer. In 2011, the NCCN published updates to include patients with TNBC diagnosed at < 60 years of age and breast cancer patients with more than two close blood relatives with pancreatic cancer at any age[13]. The intrinsic subtype of breast cancer is also being considered in addition to FH as a prerequisite to determine the need for BRCA1/2 genetic testing.

The NCCN guidelines recommend genetic counseling for patients < 50 years of age. However, in the present study the median age of all breast cancer patients was 52.2 years old; thus, 554 (60.1%) patients were eligible for counseling. This number is relatively large and impractical. We then modified the age criterion to < 40 years of age, which resulted in 313 (34%) patients who were eligible for counseling. Using this modified age criterion, we were able to identify 80% of all patients with BRCA1/2 mutations in the present study. Therefore, this modification seems to be appropriate for Japanese women. Notably, the NCCN guidelines also recommend that a separate FH for both paternal and maternal lines is obtained. However, there was not sufficient information in our clinical database to meet this criterion; therefore, the actual rate of a positive FH may be larger than estimated.

The NCCN guidelines recommend BRCA1/2 genetic testing for patients with TNBC <60 years of age. In the present study, most TNBC patients who underwent genetic testing were < 60 years of age (16/17; 94.1%). In this patient subgroup, BRCA1/2 mutations were detected in 18.6% of patients (11/59), whereas in those < 50 years of age the rate of the mutation was 23.3% (10/43). Thus, although the frequency of BRCA1/2 mutations in TNBC patients is high,

the rate tended to be higher in the lower age cut-off subgroup.

Previous studies from Japan have reported similar frequencies of BRCA1 and BRCA2 mutations[18–20]. However, in the present study, the BRCA1 mutation was observed more frequently than the BRCA2 mutation. The most likely explanation for this difference is the selection criteria used for BRCA1 / 2 genetic testing. In previous studies, the eligibility for testing was based primarily on FH, whereas in the present study TNBC was considered as an additional eligibility criterion for screening for BRCA1 / 2 mutations.

In the present study, TNBC patients with an FH of breast or ovarian cancer frequently had BRCA1 / 2 mutations (9 / 13 ; 69.2%). These nine patients with mutations represented 31% of TNBC patients with a positive FH. Similar to the findings of the present study, a previous study exploring the BRCA1 / 2 mutation frequency in the Greek population reported that, of a total of 403 patients with TNBC, 50 of 105 patients with an FH of cancer (48%) also had BRCA1 / 2 genetic mutations[21].

In the present study, two rearrangement mutations in BRCA1 were observed. In patients from high-risk families, an intragenic rearrangement prevalence of 2% and 12% for each mutation has been suggested[22–25]. In 2011, Sluiter and van Rensburg reported that 81 rearrangements of BRCA1 had been found worldwide[22]. The frequency of these rearrangement mutations varies in different races. Notably, although rearrangement mutations in Asian and Hispanic populations have been reported, they are relatively more frequent in Caucasians[23–25]. Although direct sequencing is the standard method used for BRCA1 / 2 genetic testing, this method cannot detect rearrangement mutations. Thus, when no mutation is detected by the direct sequencing method, the MLPA test should be considered for the detection of BRCA1 / 2 genetic rearrangements in high-risk patients. Indeed, the current procedures for BRCA1 / 2 genetic testing vary among countries, so there is some possibility that rearrangement mutations are missed, which would create difficulties when assessing differences in the frequency of these mutations in different populations[26, 27].

Significantly, determination of BRCA gene status is important not only in addressing the risk of breast and ovarian cancer, but also in selecting therapies. DNA-damaging cytotoxic chemotherapies and poly (ADP-ribose) polymerase (PARP) inhibitors have recently been evaluated in germline BRCA mutation carriers[28, 29]. PARP1 inhibitors have been demonstrated to elicit synthetic lethality in combination with BRCA1 / 2 dysfunction in homologous recombination-deficient breast cancers. More recently, a Phase Ⅲ clinical trial of a PARP inhibiter in combination with standard chemotherapy for TN metastatic breast cancer showed no significant difference in overall survival compared with standard chemotherapy alone[30]. It is interesting to speculate whether the results may have been different if the participants had been preselected for BRCA1 / 2 mutations. Thus, further investigations are needed to determine whether BRCA1 / 2 mutations can predict therapeutic benefit from PARP inhibitors in the treatment of TNBC.

Together, the results of the present study suggest that the estimated prevalence of BRCA1 / 2 mutations in the Japanese population is not less than that in Caucasian populations. Thus, although breast cancer tends to occur at a younger age in Japanese than Caucasian popula-

tions, guidelines like those of the NCCN appear to be suitable for predicting the occurrence of BRCA1 / 2 mutations in Japanese women. In conclusion, although the number of patients in the present study was small, the data show a high BRCA1 / 2 mutagenesis rate in TNBC patients, especially in those < 60 years of age or in combination with an FH of breast and/or ovarian cancer, as in Caucasian women. We suggest these subsets of Japanese breast cancer patients meet the threshold for BRCA testing, as outlined in the NCCN guidelines.

This study was approved by the Institutional Review Board of Showa University.

Conflict of interest

The authors have no conflicts of interest to declare.

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