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ARTICLE

The relationship between *BRCA*-associated breast cancer and age factors: an analysis of the Japanese HBOC consortium database

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Abstract

BRCA1/2 pathogenic variant prevalence in Japanese breast cancer is unclear. Here, we analyzed *BRCA1/2* pathogenic variant prevalence with a particular focus on age factors, using the Japanese HBOC consortium database. All registered subjects were Japanese individuals who underwent *BRCA1/2* genetic testing from January 1996 to July 2017 according to the Japanese HBOC consortium database. Cases were extracted and analyzed for each evaluation item. Overall *BRCA1* and *BRCA2* pathogenic variant prevalence was 11.2% and 9.0% in the cohort of 2366 proband patients, respectively. The age at onset of breast cancer for patients with *BRCA1/2* pathogenic variants was significantly lower than that for patients without a *BRCA1/2* pathogenic variant. In both *BRCA1/2* patients, ages at onset were not statistically significantly different between two subtype groups (ER-positive vs. TNBC). We analyzed the *BRCA1/2* pathogenic variant prevalence among age groups in patients with no family history of breast or ovarian cancer. In the TNBC group, the rate of genetic variants was more frequent among younger patients. Our results demonstrated that early breast cancer onset is associated with a *BRCA1/2* pathogenic variant in the Japanese population. Younger TNBC patients were more likely to have a *BRCA1/2* pathogenic variant irrespective of a family history of breast or ovarian cancer.

Introduction

Breast cancer is the most commonly diagnosed cancer in both developed and less-developed countries. Various risk factors for breast cancer such as age, reproductive history, and lifestyle factors have been known [1], however, the causes of individual breast cancers are mostly unknown. Furthermore, ~10% of breast cancer cases are thought to be hereditary, and about 25% of these are caused by inherited variants in the tumor suppressor genes *BRCA1* and *BRCA*2 (*BRCA1/2*) [2, 3]. Hereditary breast and ovarian cancer syndrome (HBOC) is an autosomal dominant inherited cancer susceptibility disorder caused by deleterious germline variants in *BRCA1* or *BRCA*2. Nowadays, about 1 in 8 women in the U. S. (about 12.8%) and 1 in 10 Japanese women (about 10.2%) will develop infiltrated breast cancer over the course of their lifetime [4, 5]. In contrast, retrospective studies suggest an estimated cumulative risk of breast cancer to 70 years of age of 40–87% for *BRCA1* variant carriers and 27–84% for *BRCA2* variant carriers [3, 6–14]. There have been various reports from around the world on the statistics for each race, but in many cases the detailed statistics have not been disclosed for the Japanese population.

In October 2012, the Japanese HBOC Consortium (JHC) was established to raise awareness about HBOC and to provide integrate healthcare for patients with HBOC and their families in Japan. We established a registration committee for JHC in October 2013 and pushed it forward as a nationwide registration project. The first report from JHC was published by Arai et al., and they reported genetic and clinical characteristics in Japanese patients with HBOC [15].

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This database is becoming increasingly crucial for HBOC research in Japan as the number of cases increases each day.

One of the clinical characteristics of hereditary tumors is its early age of onset. As it is also one of the Lynch syndrome criteria [16, 17], young-onset disease has been revealed as a very important clinical feature in hereditary breast cancer [18, 19]. It has been reported that women with germline mutations are more prone to develop breast cancer at a younger age with more aggressive subtypes than those without germline variants [20–22], but almost all reports are from foreign countries; only a few studies have used the Japanese cohort.

Here, we analyzed the cases of *BRCA*-associated breast cancer with *BRCA1/2* germline pathogenic variants registered in the JHC database. We especially focused on age factors.

Patients and methods

Study registration

The subjects enrolled were all Japanese patients who underwent *BRCA1/2* genetic testing from January 1996 to July 2017 in the participating facilities of the JHC. Ethical approval for this study was obtained from the Ethical Review Boards of the JHC and each institution. Written informed consent was obtained from all subjects. From all the registered cases, we extracted and analyzed the data from patients who have information such as their age at breast cancer onset, family history, and pathological features, that were required for each analysis.

BRCA1 and *BRCA2* gene testing

All *BRCA1* and *BRCA2* genetic testing (sequence and large rearrangement analysis) were performed at Myriad Genetic Laboratories or FALCO Biosystems. The detected variants were interpreted according to the criteria of Myriad Genetic Laboratories.

Clinical subtypes of *BRCA*-related breast cancer

Based on the registered clinical data, we examined what subtypes of cancer were frequently observed in Japanese *BRCA1/2* mutation carriers. Subtypes were determined based on estrogen receptor (ER), progesterone receptor, and human epidermal growth factor-2 (HER2) Immunohistochemistry (IHC) status. If the HER2 IHC result is 2+ and equivocal, the Fluorescence In Situ Hybridization assay for determination of HER2 status was performed. Since very few HER2-positive cases were found, this study compared the ER-positive (ER+) group and the triple-negative breast cancer (TNBC) group.

Statistical analysis

Statistical significance was analyzed by one-way analysis of variance and the Student's t test using R software (http:///www.rproject.org/) and Bioconductor (http://bioconductor.org/). Results were considered statistically significant at $p < 0.05$.

Results

Patient demographics and variant prevalence in the JHC cohort

The total number of registrations is 11,711 Japanese individuals between January 1996 and August 2017, including their relatives who have not received genetic testing.

Out of all those registered, 2366 cases were the probands who underwent genetic testing, and the pathogenic variant detection rate was evaluated only for these cases. As a result, 265 (11.2%) cases had a *BRCA1* pathogenic variant, 214 (9.0%) cases had a *BRCA2* pathogenic variant, and 3 (0.1%) cases had both *BRCA1* and *BRCA2* pathogenic variants (Fig. 1). This database includes 2054 female patients with breast cancer, 89 female patients with ovarian cancer patients, 62 female patients with both breast and ovarian cancers, 14 male breast cancer patients, and 147 individuals who had neither breast nor ovarian cancer. We compared the rate of each cohort with previous reports [23–37] (Table 1).

Age of breast cancer onset is lower in patients with *BRCA1/2* pathogenic variants

Since the age of cancer onset is one of the most important characteristics of hereditary breast cancer, we investigated whether it was associated with the presence or absence of the *BRCA1/2* variant.

In our database, there were 3891 cases who underwent genetic testing and whose data clearly reported age of onset. Figure 2 and Supplementary Table 1 show the distribution of age at onset for breast cancer among different age groups. The general statistical data for comparison were data from the 2017 Japanese cancer statistics [38]. The mean age of onset was 43.6, 45.2, 48.8 years in the *BRCA1* variant group, *BRCA2* variant group, and *BRCA1/2* pathogenic variant free groups, respectively (Table 2). A statistically significant earlier age of onset was observed in the group of patients with the *BRCA1/2* pathogenic variant compared to the group of patients without the *BRCA1/2* pathogenic variant (Table 2).

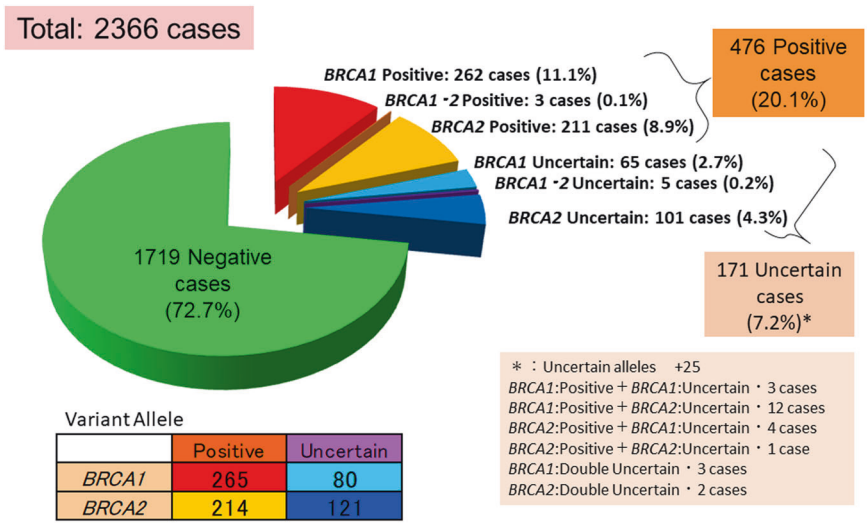

Fig. 1 The prevalence of *BRCA1* and *BRCA2* variant among the cases who underwent the screening test. The total number of cases was 2366

Table 1 Comparison with previous reports

Study	Country	Year	Race	High-risk or sporadic	Total	*BRCA1*+		*BRCA2*+		*BRCA1/2*+		Reference
						Cases	(%)	Cases	(%)	Cases	(%)	
Sugano et al.	Japan	2008	Japanese	h	122	16	(13.1)	18	(14.8)	34	(27.9)	[23]
Hall et al.	USA	2009	Mixed	h	46,276	3351	(7.2)	2444	(5.3)	5795	(12.5)	[26]
Weitzel et al.	USA	2012	Mixed	h	746	124	(16.6)	65	(8.7)	189	(25.3)	[27]
Couch et al.	USA	2015	Mixed	h	1824	155	(8.5)	49	(2.7)	204	(11.2)	[25]
Kang et al.	South Korea	2015	Korean	h	2403	157	(6.5)	224	(9.3)	378	(15.7)	[31]
Kast et al.	Germany	2016	Germany	h	59,304	10,195	(17.2)	5542	(9.3)	15,737	(26.5)	[32]
Kemp et al.	UK	2019	NA	h	1184	57	(4.8)	60	(5.1)	117	(9.9)	[37]
Okano et al.	Japan	2020	Japanese	h	2,366	262	(11.1)	211	(8.9)	476	(20.1)	
Tung et al.	USA	2015	Mixed	mixed	1,781	78	(4.4)	87	(4.9)	165	(9.3)	[30]
Buys et al.	USA	2017	Mixed	mixed	35,409	814	(2.3)	828	(2.3)	1642	(4.6)	[34]
Palomba et al.	Italy	2014	Italian	s	726	7	(1.0)	14	(1.9)	21	(2.9)	[28]
Ghadirian et al.	Canada	2014	French-Canadian	s	1093	13	(1.2)	43	(3.9)	56	(5.1)	[29]
Susswein et al.	USA	2016	Mixed	s	5209	63	(1.2)	73	(1.4)	136	(2.6)	[33]
Wen et al.	Malaysia	2017	Asian	s	2575	55	(2.1)	66	(2.6)	121	(4.7)	[35]
Momozawa et al.	Japan	2018	Japanese	s	7051	102	(1.45)	191	(2.71)	293	(4.16)	[36]

In both *BRCA1/2* positive patients, age at onset did not statistically differ between ER-positive group and TNBC group

Furthermore, we examined the relationship between the breast cancer clinical subtype and each *BRCA1/2* pathogenic variant using a group of patients with subtype information. In our cohort, 971 ER+ patients and 515 TNBC patients had IHC information that could be analyzed. The mean age at breast cancer onset of patients with the *BRCA1* pathogenic variant, with the *BRCA2* mutation, and without the *BRCA1/2* pathogenic variant in the ER+ group were 41.6, 41.8, and 46.4 years, respectively. There was a statistically significant difference in the age of onset between the group with *BRCA1/2* variant and the group without BRCA1/2 variant in both ER+ and TN subgroup ($p < 0.01$). In TNBC group, the average ages were 40.8, 41.7, and 45.6 years, respectively. There was no statistically significant difference between the two subtype groups in each group (Table 3).

The prevalence of pathogenic variants is more frequent among younger patients in the TNBC group even with no family history

The relationship between subtype and age with no family history is also interesting. We analyzed the prevalence of

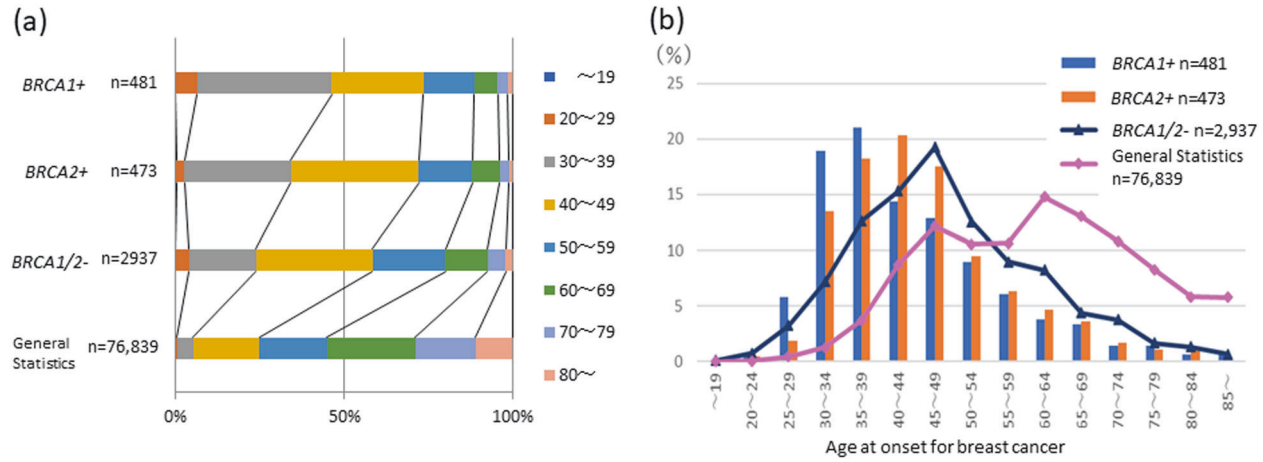

Fig. 2 **a** Comparison of frequency distribution by age at onset of breast cancer in cases with or without *BRCA1/2* variants and the general statistics. **b** Age distribution of the cases with or without *BRCA1/2* variants

Table 2 The mean of age onset of each group

Gene variant	*n* (%)	Age at onset (year)		Pairwise comparison *p* value		
		Mean ± SD	Range	*BRCA1+*	*BRCA2+*	*BRCA1/2−*
BRCA1+	481	43.6 ± 12.5	21–99	–		
BRCA2+	473	45.2 ± 11.1	19–84	0.0175	–	
BRCA1/2−	2937	48.8 ± 12.6	17–95	<0.001	<0.001	–

SD standard deviation

Table 3 Subtype details and onset age in each *BRCA* condition

Gene variant	Subtype	*n*	Age at onset		*p* value
			Mean ± SD	Range	
BRCA1+	Luminal	30	41.6 ± 10.7	25–71	NS
	TNBC	147	40.8 ± 9.8	23–75	
BRCA2+	Luminal	97	41.8 ± 9.5	23–73	NS
	TNBC	25	41.7 ± 12.3	19–71	
BRCA1/2−	Luminal	844	46.4 ± 10.5	22–83	NS
	TNBC	343	45.6 ± 11.6	22–85	

SD standard deviation

pathogenic variants among age groups in cases with no family history of breast and ovarian cancer. There were 246 ER+ cases and 211 TNBC cases in the cohort where we extracted patients that had no family history and had the onset age and subtype information.

Figure 3 and Supplementary Tables 2 and 3 show that the rate of *BRCA1/2* pathogenic variant showed no trend by age in the ER-positive group. On the other hand, the prevalence of pathogenic variants was higher among younger patients in the TNBC group. Also, no variant in both genes was observed in this analysis past the age of 60.

Discussion

The purpose of this study was to characterize breast cancer patients with *BRCA1/2* variants in a Japanese-only cohort, with a particular focus on age factors. To date, only a few studies have examined the details of the prevalence of *BRCA1/2* variants in a Japanese-only cohort.

In Japan, Sugeno et al. were the first to report the prevalence of *BRCA1/2* variants. In the study, the prevalence of deleterious variants in a cohort of Japanese women was considered to be about 1.9 times higher than that in non-Ashkenazi American women, provided that background factors such as medical history and family history are similar [23, 24].

In our result, the prevalence rate in a Japanese high-risk cohort has decreased (27.9–20.1%) with the increase in the size of the cohort, which is closer to the actual clinical situation. Nonetheless, one in five in the Japanese high-risk group still had *BRCA1/2* variants. This seems to be a slightly higher rate than reports from other countries analyzing high-risk cohorts (Table 1). It is highly likely that our cohort included the cases with higher risk because *BRCA1/2* genetic testing was not covered by the national health insurance in Japan, until recently. Now that the tests are covered by national health insurance, further studies are required.

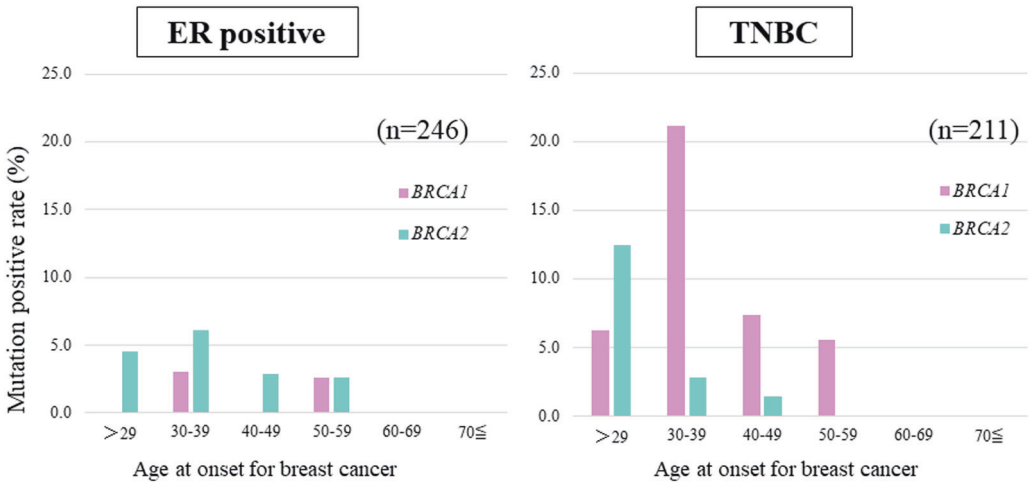

Fig. 3 The prevalence of *BRCA1* and *BRCA2* variants stratified by subtype and age groups in the cases with no family history of breast or ovarian cancer. Red bars indicate *BRCA1* variants and blue bars indicate *BRCA2* variants

Momozawa et al. investigated the prevalence of *BRCA1/2* variants in sporadic breast cancer cohort and control cohort of healthy women in 2018 [36]. According to this report, the prevalence of *BRCA1/2* variants in 7051 Japanese patients with breast cancer was about 4.16%, which was clearly lower than our data. Although it is important to investigate the prevalence of gene mutations in sporadic breast cancer, in clinical practice, our data, which includes many high-risk cases, are more likely to be useful when clinicians consider whether genetic testing should be recommended for individual cases with suspected familial breast cancer based on these factors: clinical presentation, family history, age, and subtype.

The age factor is one of the testing criteria of the NCCN guidelines for familial breast and ovarian cancer [39]. Although it is clear that there is a strong association between familial breast cancer and a younger onset of the disease, it has also been reported there were differences among races and ethnicities [26, 40] in this aspect. There are reviews from various races, but many have no clear family history, or the cohort conditions are different [41]. It is necessary to confirm the details in a large cohort of the Japanese population. Our data showed that breast cancers with *BRCA1/2* mutations were also diagnosed at a younger age in a Japanese cohort, and particularly those with *BRCA1* mutations had a younger age at onset (43.6 years). Compared to the previous reports, the age of onset in BRCA patients of our cohort was slightly higher than those of previous studies (around 42 years) [42, 43]. Study populations of these reports consisted of dominantly Caucasian/white patients. The racial differences about the effect of BRCA variants on the age of onset or other clinical characteristics have been largely unknown. Thus, further studies, especially in non-Caucasian race populations, are warranted for the better understanding of clinical features of BRCA variants.

There have been many reports of the association between *BRCA*-related breast cancer and its subtypes. Several studies have demonstrated that *BRCA1*-associated tumors are usually TNBC and *BRCA2* mutation carriers commonly develop ER-positive breast cancer [43–45]. A similar pattern was reported in metastatic and recurrent breast cancer [46]. However, only a few reports have included age factors. Data from Singapore showed that TNBC patients with *BRCA1* variants were diagnosed at a relatively younger age than non-TNBC patients with the same gene variants (38 vs. 46 years, $p = 0.028$) [47]. On the other hand, there was no difference in the age of onset between luminal type BC and TNBC in our present study (both around 41 years) (Table 3). Though both cohorts are Asian and high-risk groups with a family history and/or early onset, this discrepancy may have occurred due to differences in race and other environmental factors.

Furthermore, our data showed that TNBC onset in a patient's fourth decade of life can have *BRCA1* variants in more than 20% of those without family history, even in a Japanese cohort. On the other hand, no cases had *BRCA1/2* variants in patients over 60 years with no family history of breast and ovarian cancer in our cohort. The data from Tung et al. and Momozawa et al. showed that the prevalence of pathogenic variants in breast cancer-related genes in patients aged 60 and older is 6.4% and 4.1%, respectively, but these data may include cases with a family history [36, 42]. A study from Germany showed that there was a 6.9% prevalence of *BRCA1/2* variants in TNBC patients aged 60–69 years [48] where the authors concluded that TNBC patients diagnosed before the age of 50 years with no familial history of breast and ovarian cancer should be tested for *BRCA* variants. A report by Cough et al. demonstrated that the prevalence of *BRCA1/2* variants in patients without a family history that are 60 years older in

Western populations was only 2%, even in TNBC. Although the number of TNBC patients without family history of breast and ovarian cancers were limited in our cohort and the results should be confirmed in larger studies, this information could potentially reduce the number of patients undergoing tests that bring no potential benefit. In addition, although it is now covered by national health insurance, a *BRCA1/2* gene test costs around 2000 USD in Japan. Considering that about 86% of Japan's national health expenditure is covered by public medical insurance and medical expenses are increasing annually, it is better to avoid unnecessary genetic testing. The availability of olaparib, which has proven to be effective for the treatment of HER2-negative metastatic breast cancer with a pathogenic variant in *BRCA1/2* [49], has steadily increased the number of germline gene variant tests. *BRCA* genetic testing is recommended in any age for the use of olaparib in HER2-negative metastatic breast cancer. It is therefore necessary for health care professionals to provide correct information and appropriate genetic testing for their patients, which would have both clinical and economic benefits.

This study has some limitations. A major limitation of our study is the relatively small cohort. It is expected that more cases will be registered since *BRCA1/2* pathogenic variant testing is now covered by national health insurance in Japan. Second, as mentioned above, there is a possibility of the bias that there are more patients at higher risk. Due to the high cost of genetic testing, patients who are not high-risk may have refrained from genetic testing in Japan. Breast cancers with *BRCA2* variants have a higher age of onset than breast cancers with *BRCA1* variants [50] and have weaker hereditary cancer characteristics, which may reduce its proportion in high-risk cohorts. These data can be seen in Table 1.

Conclusion

Our data indicate that breast cancer with a *BRCA1/2* mutation has an early onset even in the Japanese population. Furthermore, more than 20% of young TNBC patients had a *BRCA1/2* mutation even if they have no family history of breast and ovarian cancer.

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Compliance with ethical standards

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

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