Efficacy of clinical guidelines in identifying all Japanese patients with hereditary breast and ovarian cancer

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Research Article

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Abstract

Purpose

Clinical screening using the National Comprehensive Cancer Network (NCCN) testing criteria may fail to identify all patients with hereditary breast and ovarian cancers. Thus, this study aimed to evaluate the strategy of expanding target patients for genetic testing among Japanese patients.

Patients and Methods

We reviewed the medical records of 91 breast cancer patients who were genetically tested.

Results

Among 91 patients, eight were diagnosed with pathogenic or likely pathogenic variants: *BRCA1* (n=4) and *BRCA2* (n=4). Among 50 patients meeting the testing criteria of the guideline, six (12%, 95% confidence interval; 4.5–24.3%) were diagnosed with pathogenic or likely pathogenic variants. The sensitivity and specificity of screening using the testing criteria were 75% and 47%, respectively. Expanding the NCCN criteria to include all women diagnosed with breast cancer aged ≤ 65 years achieved 88% sensitivity but 8% specificity.

Conclusions

The expansion of the NCCN criteria could benefit Japanese patients.

Introduction

The National Comprehensive Cancer Network (NCCN) recommends the identification of high-risk patients in the testing of hereditary breast and ovarian cancer (HBOC), followed by germline genetic testing. This practice is reasonable from a medico-economic perspective because genetic testing is expensive.

A study on HBOC conducted in the United States (US) showed that clinical screening using the NCCN criteria may fail in identifying all patients with HBOC [1]. In particular, the usefulness of genetic testing for all patients with breast cancer aged under 65 years rather than screening with the testing criteria was suggested [1]. The price of genetic testing is decreasing; thus, the feasibility of this strategy is also increasing. As shown in the aforementioned study, it is also possible to expand the target group for genetic testing in Japan. However, the prevalence of and the age at the onset of the disease may differ between Japan and Western countries, and thus, the usefulness of this strategy needs to be evaluated using data from Japan.

In Japan, *BRCA1/2* genetic testing has been available as a companion diagnostic testing for molecular target agents since 2018. Patients who are candidates for these agents can undergo this testing without screening with the traditional testing criteria by NCCN [2]. Thus, the number of these patients is

increasing. This study aimed to evaluate the conventional strategy for screening for genetic testing using the NCCN testing criteria in Japanese patients.

Patients And Methods

We retrospectively reviewed the medical records of 91 breast cancer patients who underwent genetic testing for *BRCA1/2* as a companion diagnostic testing for olaparib at Kanagawa Cancer Center from October 2018 to December 2019. According to the indication for olaparib, all 91 patients had HER-2-negative advanced or relapsed breast cancer. The patients were divided into two groups: those identified as high-risk patients for genetic testing using the *BRCA1/2* testing criteria of NCCN Guidelines® for Genetic/Familial High-Risk Assessment: Breast and Ovarian Version 3.2019 and those who did not meet these criteria [3]. This study was approved by the institutional review board of the Kanagawa Cancer Center (2019-126).

In this study, we partially modified the *BRCA1/2* testing criteria according to our clinical practice at Kanagawa Cancer Center, as described elsewhere [4]. Briefly, patients with unknown family history or relatives with unknown cancer pathology who could not be determined to be in the high-risk group were included in the low-risk group. According to the NCCN criteria, patients with a diagnosis of breast cancer aged under 45 years were included in the high-risk group regardless of family history. In this modification, the age was set to 40 years or younger. Sensitivity and specificity were calculated to evaluate the usefulness of the guidelines. The relationship between meeting the criteria and testing results was evaluated using Fisher's exact test. Statistical analyses were performed using EZR on R commander, version 1.4 [5]. For all analyses, p-values<0.05 were considered statistically significant.

Results

Among 91 patients including 2 men and 89 women, eight were diagnosed with pathogenic or likely pathogenic variants: *BRCA1* (n=4) and *BRCA2* (n=4) **(Table 1).** Among 50 patients who met the testing criteria of the guideline, six (12%; 95% confidence interval 4.5–24.3%) were diagnosed with pathogenic or likely pathogenic variants. Among 41 patients who did not meet the testing criteria, two (4.9%; 95% confidence interval 0.1–0.5%) were diagnosed with pathogenic or likely pathogenic variants. No statistically significant relationship was found between meeting the criteria and testing results (odds ratio 2.6; p=0.28) (**Table 2**). One patient with a *BRCA1* pathogenic variant was diagnosed with triple-negative, unilateral breast cancer when she was aged 72 years. She has a sister who developed breast cancer in her early 60s. The other patient was diagnosed with hormone receptor-positive breast cancer when she was aged 62 years. Her family history did not include breast cancer, ovarian cancer, pancreatic cancer, or prostate cancer. The sensitivity (75%) and specificity (47%) of screening using the testing criteria are shown in Table 2. Expansion of the NCCN criteria to include all women diagnosed with breast cancer and aged ≤65 years achieved 88% sensitivity; however, the specificity was 8% (**Table 2**).

Discussion

This study showed that some patients with *BRCA1/2* pathogenic variants or likely pathogenic variants could be missed by screening using the NCCN testing criteria in Japan, consistent with a previous study in the US [1]. The expansion of NCCN criteria is worth investigating in Japanese patients, including providing genetic testing for all patients under a certain age.

The optimal age threshold for providing genetic testing for all patients under that age was unclear. In this study, a higher threshold for age indicated lower specificity. An investigation from the perspective of medical economics is required to evaluate the usefulness of this expansion strategy. In the patients who met the NCCN testing criteria and who did not, testing about nine (8.3) and 21 patients, respectively, was necessary to identify one patient with *BRCA1/2* pathogenic or likely pathogenic variant. With health insurance in Japan, genetic testing for *BRCA1/2* costs 202 000 JPY (1 867 USD).

This indicates that it costs 1 676 600 JPY (15 500 USD) and 4 242 000 JPY (39 217 USD) to identify one patient with *BRCA1/2* pathogenic or likely pathogenic variants, respectively. The lower threshold of age indicates a lower cost of identifying one patient. Therefore, when deciding on the age range, we must consider the medico-economic and public health aspects of appropriate expenditure.

This study had some limitations. First, the sample size was small. Second, this study included patients with advanced or relapsed breast cancer. Usually, many patients with breast cancer undergo genetic testing before surgery. Thus, the background of the patients between patients in this study and general patients receiving genetic testing in medical practice may differ; the ratio of triple-negative breast cancer could be higher in this study [6].

In conclusion, the expansion of NCCN criteria could benefit Japanese patients, by additionally providing genetic testing for all patients under a certain age, preferably 65 years.

Declarations

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Tables

Table 1: Characteristic of the patients

Characteristic	Total (N = 91)	Meeting NCCN Criteria* (n = 50)	Not Meeting NCCN Criteria (n = 41)
Age at diagnosis of first breast cancer, years			
Median	52***	48***	58
≤29	2	2	0
30-39	14	14	0
40-49	26	15	11
50-59	24	10	14
60-69	17	7	10
70-79	8	2	6
Subtype**			
Triple negative	23	13	10
Luminal	68	37	31
Personal history of other cancers			
Any cancer	5	2	3
Ovarian	0	0	0
Pancreatic	1	1	0
BRCA1/2			
BRCA1 pathogenic or likely pathogenic variants	4	3	1
BRCA2 pathogenic or likely pathogenic variants	4	3	1
No pathogenic or likely pathogenic variants	83	44	39

*We used revised criteria. Patients with unknown family history or relatives with unknown cancer pathology who could not be determined to be in the high-risk group were included in the low-risk group. According to the NCCN criteria, patients with a diagnosis of breast cancer aged under 45 years were included in the high-risk group regardless of family history. In this modification, this age was set to 40 years or younger.

**All of the 91 patients had HER-2 negative breast cancer.

***One patient was excluded due to lack of exact information of age.

Table 2: Sensitivity and specificity

	Patients with pathogenic or likely pathogenic variants	Patients without pathogenic or likely pathogenic variants	Sensitivity	Specificity
Meeting NCCN testing criteria or age at diagnosis, years				
Meeting NCCN testing criteria	6	44	0.75	0.47
Not meeting NCCN testing criteria	2	39		
Meeting NCCN testing criteria or ≤50 years old	6	55	0.75	0.34
Not meeting NCCN testing criteria and >50 years old	2	28		
Meeting NCCN testing criteria or ≤55 years old	6	61	0.75	0.27
Not meeting NCCN testing criteria and >55 years old	2	22		
Meeting NCCN testing criteria or ≤60 years old	6	71	0.75	0.14
Not meeting NCCN testing criteria and >60 years old	2	12		
Meeting NCCN testing criteria or ≤65 years old	7	76	0.88	0.08
Not meeting NCCN testing criteria and >65 years old	1	7		
Meeting NCCN testing criteria or ≤70 years old	7	78	0.88	0.06
Not meeting NCCN testing criteria and >70 years old	1	5		
Meeting NCCN	8	81	1.00	0.02

testing criteria or ≤75 years old		
Not meeting NCCN testing criteria and >75 years old	0	2

*We used the revised criteria.