

Current condition of genetic medicine for hereditary breast cancer

HIROKO TERUI-KOHBATA^{1,2} and MASAYUKI YOSHIDA^{1,2}

¹Bioethics Research Center, Tokyo Medical and Dental University; ²Division of Medical Genetics, Medical Hospital of Tokyo Medical and Dental University, Tokyo 113-8510, Japan

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Abstract. *BRCA1* or *BRCA2* (*BRCA1/2*) germline mutations, which cause hereditary breast and ovarian cancer syndrome, have been studied to develop targeted therapies for these associated cancer types. The *BRCA1/2* test has been implemented in more than one hundred medical facilities in a clinical setting in Japan. The purpose of the current study is to document the prevalence and the awareness of genetic medicine for all hereditary breast cancer (HBC) including the *BRCA1/2* test in Japan. The self-administered questionnaire was sent to 120 medical facilities where the *BRCA1/2* test was provided, and 83 health care professionals participated (response rate, 69.2%). Of the all respondents, 33.7% (N=42) were clinical geneticists, 31.3% (N=26) other physicians, 15.7% (N=13) genetic counselors and 2.4% (N=2) nurses. In the most recent one-year period, in 83.1% of the 69 facilities the number of patients who underwent genetic testing for HBC was <10 and only 4 facilities provided multigene panel testing for HBC. In order to facilitate the access to genetic medicine, the majority of the genetic counselors (58.3%) recognized the need for education of healthcare professionals. Although the awareness of and interests in HBC have increased gradually, the equitable access to precision medicine is considered to be a challenging issue in Japan.

Introduction

The number of individuals affected with breast cancer has increased globally. In Japan, 89,400 females were newly diagnosed with breast cancer and there were 13,800 mortalities attributed to this disease in 2015 (1). Approximately 20% of breast cancer patients have a family history and 5-10% (2,3)

are considered to be hereditary (hereditary breast cancer) HBC caused by a germline mutation such as *BRCA1*, *BRCA2*, *TP53* or *PTEN*. Mutations in *BRCA1/2* genes are associated with hereditary breast and ovarian cancer syndrome (HBOC), which is the most common form of HBC. It is also known that germline mutations of DNA mismatch repair (MMR) genes, such as *MLH1*, *MSH2* and *MSH6* are caused by Lynch syndrome, which is a hereditary colorectal cancer syndrome, and *MLH1* particularly increases the risk of breast cancer (4).

Women with HBOC have a 41-90% lifetime risk of developing breast cancer (5) and HBOC is characterized by the high risk of contralateral breast cancer (6). In addition, the cumulative risk for ovarian cancer is 8-59% and is higher in *BRCA1* mutation carriers compared with *BRCA2* mutation carriers (5-7). It was revealed that triple-negative breast cancer, which is estrogen receptor/progesterone receptor-negative and human epidermal growth factor receptor 2, negative was associated with HBOC and that 36% of women with early-onset triple-negative breast cancer (aged <40 years) had a *BRCA1* mutation and 27% of women with triple-negative breast cancer diagnosed before the age of 50 years had a *BRCA1* mutation (8). Male *BRCA1/2* mutation carriers are also at increased risk of cancer. The cumulative risk of breast cancer is 1.2% in male *BRCA1* mutation carriers and 6.8% in male *BRCA2* mutation carriers (9), and the risk of prostate cancer of *BRCA2* mutation carriers is increased to ~3 times higher than that of the general population (10,11). Owing to the early onset and susceptibility of multiple cancer associated with HBOC, the importance of surveillance from a younger age has been emphasized (12). For female carriers of a *BRCA1/2* mutation, a monthly breast self-examination from the age of 18, an annual breast MRI or mammography between the ages of 25 and 29 and an annual breast MRI and mammography over 30 years of age are recommended. However, the usefulness of surveillance programs for cancer risks is not clear, and an appropriate screening method has not been established. Therefore, once a *BRCA1/2* mutation is identified in cancer patients and their families, the option of the risk reducing mastectomy (RRM) and the risk reducing bilateral salpingo-oophorectomy (RRSO) must be considered. In the retrospective study, the 20-year survival rate for females with a *BRCA1/2* mutation who underwent contralateral prophylactic mastectomy was 88% and for those who did not was 66% (13). Also, the results of meta-analysis revealed that RRSO reduced ovarian cancer risk by 80% and breast cancer risk by 50% in female *BRCA1/2*

Correspondence to: Dr Masayuki Yoshida, Bioethics Research Center, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan
E-mail: masa.vasc@tmd.ac.jp

Abbreviations: *BRCA1* or *BRCA2* gene, *BRCA1/2*; HBC, hereditary breast cancer; HBOC, hereditary breast and ovarian cancer syndrome

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mutation carriers (14). Furthermore, in a short-term follow-up study, RRSO reduced breast cancer-specific mortality by 90%, and gynecologic cancer-specific mortality by 95% and overall mortality by 76% (15). In addition, the use of the oral poly ADP-ribose polymerase inhibitor Lynparza™ (olaparib) for patients with advanced ovarian cancer with a *BRCA1/2* mutation was approved by the FDA in December 2014. Although the clinical trial for this drug has not yet been completed in Japan (16), it may become a promising new drug for patients with *BRCA1/2*-associated cancer once approved.

The frequency of variants of uncertain significance (VUS) on the *BRCA1/2* gene was 2-6 % in the Caucasian population in the US (17,18) and this frequency is thought to be greater in other countries with varying ethnic backgrounds due to the small number of patients undergoing *BRCA1/2* testing. Therefore proper assessment of VUS has become a major issue in clinical genetic testing. Furthermore, previous studies have demonstrated that *BRCA1/2* mutation-negative patients harbored deleterious mutations in moderate-risk cancer genes such as *CHEK2*, *ATM*, and *PALB2* and MMR (19,20). Despite an increasing number of HBC testing facilities, there is little information available regarding attitudes towards precision medicine for HBC in Japan.

Patients and methods

Study subjects and questionnaire. A total of 120 medical facilities were selected for this survey because those facilities may be confirmed on the website to be providing the *BRCA1/2* tests for patients with cancer and their families. The written information on this survey and self-administered questionnaire were sent to the facilities between September and October 2015. The questionnaire contained the following items: i) the outline of the respondents' facilities, ii) the respondents' characteristics such as their affiliation and specialty, iii) the number of clients who visited for genetic counseling and/or received genetic testing for HBC in the most recent one-year period, iv) the current status of implementation of RRM and RRSO and v) the requirements for improving access to genetic counseling. The subjects filled in the questionnaire if they consented to participate in the study. The collected data were calculated as totals, means, medians or percentages and the free descriptive answers were categorized. The study protocol was approved by the Medical Research Ethics Committee of Tokyo Medical and Dental University (Tokyo, Japan) (no. 2231).

Results

Background information of the facilities and the health care professionals. The questionnaire was sent to 120 medical facilities, and a total of 83 health care professionals participated (response rate, 69.2%). Approximately one half of the respondents belonged to university hospitals (N=40, 48.2%) and to the division of medical genetics (N=37, 44.6%), and the majority were genetics professionals (N=55, 67.3%), such as clinical geneticists and genetic counselors (Table I).

The number of clients who underwent genetic testing. In 66.3% (N=55) of the respondent's facilities, the number of

Table I. The outline of the facilities and the respondents' characteristics.

A, Summary of facility		
	N	%
Type		
University hospital	40	48.2
Cancer center	8	9.6
Other hospital	26	31.3
Clinic	8	9.6
Other	1	1.2
Number of beds		
<50	8	9.6
<100	6	7.2
<200	4	4.8
<500	19	22.9
<1,000	39	47.0
>1,000	7	8.4
B, Number of breast cancer surgeries/year		
	N	%
non-performance	8	9.6
<50	13	15.7
<200	36	43.4
<500	24	29.0
>500	2	2.4
C, Respondent's characteristics		
	N	%
Division		
Medical genetics	37	44.6
Breast surgery	28	33.7
Obstetrics & gynecology	8	9.6
Other	10	12.0
Specialty		
Clinical geneticist	42	50.6
Other physician	26	31.3
Genetic counselor	13	15.7
Nurse	2	2.4

patients who visited genetic counseling regarding HBC in the most recent one-year period was <10 (Fig. 1). In total, 24.1% (N=20) of the facilities did not perform any genetic testing (Fig. 2). Even in the facility where >100 clients visited genetic counseling, the number who received implementation of genetic testing was <50.

Of all the respondents' facilities, 60.2% dealt with only *BRCA1/2* testing and 38.6% with other targeted genetic testing.

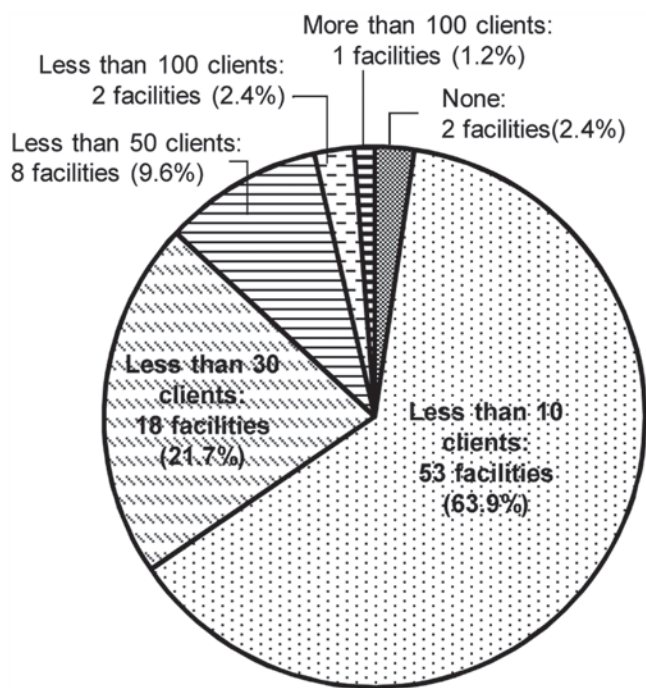


Figure 1. The number of clients who visited genetic counseling regarding hereditary breast cancer in the most recent year.

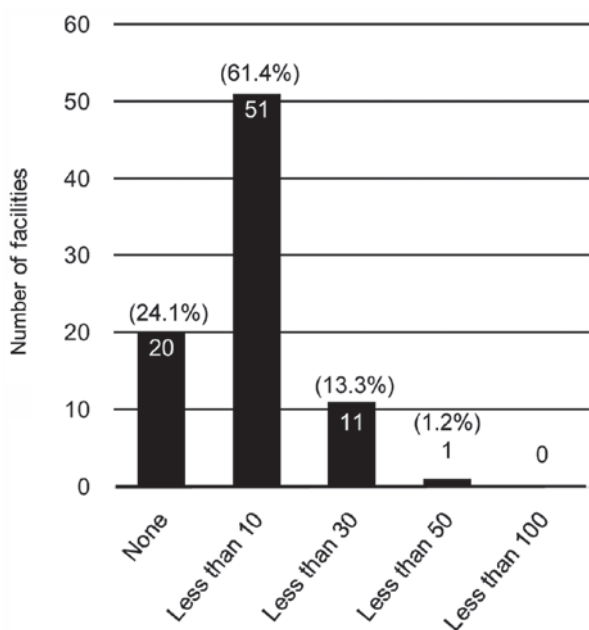


Figure 2. The number of facilities providing genetic testing regarding hereditary breast cancer.

Only four facilities (4.8%) provided multigene panel testing for HBC.

Status of implementation of RRM and RRSO. RRM was implemented in 19.3% (N=16) of the respondents' facilities and RRSO in 24.1% (N=20) but ~30% of the facilities that have not implemented RRM and RRSO are currently considering introducing these surgeries (26.9 and 28.6%, respectively) (Table II). In total, 6.0% (N=5) and 18.1% (N=15) of the

facilities, respectively, had experience in performing these surgeries and it was therefore identified that RRSO may be more frequently performed than RRM in Japan.

Access to genetic medicine. The respondents were asked about the barriers that impeded visiting genetic counseling, excluding the issues of the high-costs of genetic testing. The majority of the genetic counselors (N=7, 58.3%) recognized the need for education of medical staff in order to improve the access to genetic counseling. On the other hand, the clinical geneticists answered that the education of patients with cancer and their families (N=14, 33.3%), as well as the education of medical staff (N=14), was necessary. In addition, respondents thought of the following factors as other barriers to participating in genetic counseling: Negative feelings toward hereditary diseases (N=8), the lack of human resources such as physician's consultation time regarding HBC (N=6), and the number of genetic counselors (N=5) and the clinical and genetic data among Japanese populations (N=5).

Discussion

In the past few years, the awareness of HBC in Japan has rapidly grown, partly in reaction to the announcement of a US actress that she underwent a double mastectomy to avoid the risk of breast cancer. Nonetheless, as presented in the current study, 66.3% of facilities who responded to this survey in Japan answered that the number of clients receiving HBC-associated genetic counseling was <10 in the last year, and 24.1% answered no genetic testing was performed in the past year. As genetic screening for HBC is not covered by public health insurance in Japan, clients taking the test must pay the cost in full (~200,000 JPY). These financial burdens on patients may be one of the negative factors.

Though the pattern of occurrence of breast and ovarian cancer in a pedigree is characteristic of HBOC, a mutation in the *BRCA1/2* gene may be identified in more than ninety percent of these pedigrees (21); patients with Li-Fraumeni syndrome, Cowden syndrome and Peutz-Jeghers syndrome have a higher risk of breast cancer (22-24), and *MMR*, *CHECK2*, *PALB2* and *ATM* gene mutations also increase breast cancer risk (25). Therefore, during the genetic counseling for HBC, a risk assessment to identify the genes including *BRCA1/2* that must be examined from the patterns of cancer development in probands and within a family is essential. The current survey revealed that over sixty percent of the facilities provided the *BRCA1/2* test alone. As presented in Fig. 3, approximately one half (N=23, 47.9%) of the university hospitals and cancer hospitals offered only *BRCA1/2* tests for HBC. The services of genetic counseling and genetic testing based on a comprehensive risk assessment of HBC may not be available in these facilities. Although the multi-gene cancer panel test is very useful to analyze the causal genes for HBC, the test has not been widely used in the Japanese clinical setting.

Another issue identified by this survey is a lack of education for health care providers, patients with cancer and their families. In particular, ~60% of the genetic counselors recognized the needs for education of medical staff. Previous

Table II. The availability and use of RRM and RRSO.

	Unavailable, N (%)	Under consideration, N (%)	Available, N (%)	Number of uses (%)		
				0	<5	<10
RRM	67 (80.7)	18 (26.9)	16 (19.3)	11 (68.8)	5 (31.3%)	0 (-)
RRSO	63 (75.9)	18 (28.6)	20 (24.1)	5 (25.0)	13 (65.0)	2 (10.0)

RRM, risk reducing mastectomy; RRSO, risk reducing bilateral salpingo-oophorectomy.

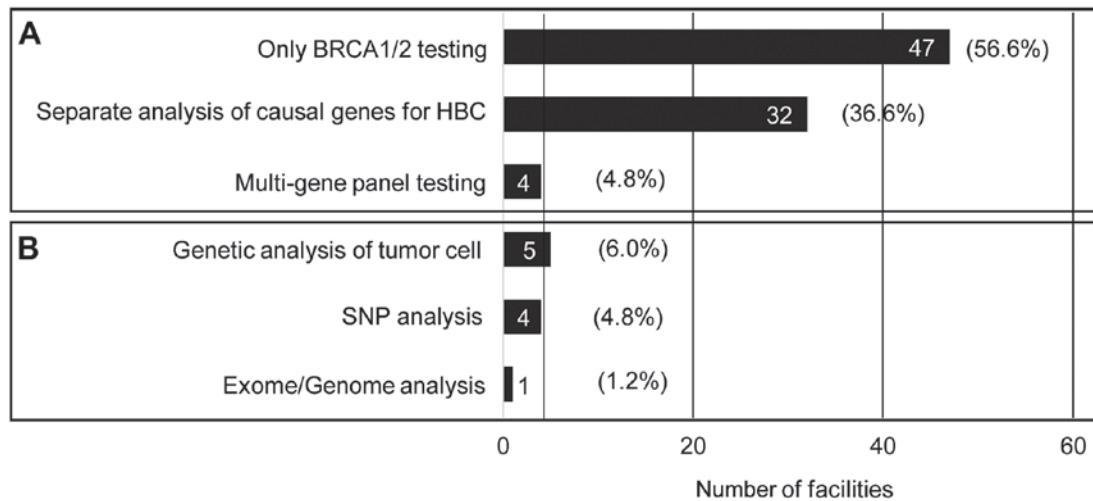


Figure 3. The type of genetic analysis of hereditary breast cancer and breast cancer. Respondents were required to select one item from (A) and to choose applicable items from (B) (multiple answers allowed) if those analyses were available in the respondents' facilities.

studies have revealed that the physicians' recommendation and referral to genetic counseling significantly affected the patients' motivation for receiving genetic counseling (26-28). Particularly in Asia, the physician's referral was a strong motivator (26-28). Accordingly, there is an urgent requirement for the additional education of physicians regarding appropriate referrals for cancer genetics.

Furthermore, certain respondents were concerned about the lack of clinical and genetic data on HBC in Japan. Only 260 individuals with a strong family history of breast cancer at 8 institutions in Japan were recorded and analyzed regarding *BRCA1/2* genes by the end of March 2012 (29). The small sample size of this study limits its clinical significance and the results of on-going study are required. Recently, the rate of VUS results among those undergoing the *BRCA1/2* genetic testing in the US has decreased 2.1% from 13%, which was accomplished by numerous efforts directed to the determining the pathogenicity of variants in over one million samples tested over 20 years (18). Therefore, accumulation of data from the Japanese population is essential for effective use of genetic testing.

The overall interpretation of VUS is currently reported in 2.1% of patients undergoing genetic analysis for HBC at Myriad Genetic Laboratories (9,10). This represents a decline from around 13% over the past decade. The dramatic decline

in the percentage of patients receiving a VUS result reflects the impact of targeted efforts directed at determining the pathogenicity of variants, as well as the availability of data from an increased number of individuals undergoing testing for HBC (10).

When a mutation is identified in patients and their unaffected family members, they are provided the option of RRM and RRSO in order to reduce future risk of cancer. However, as presented in Table II, RRM and RRSO are not available in the majority of the facilities in Japan. The current study indicates that a comprehensive medical care system is necessary to offer a wider range of options for patients.

In conclusion, the status of genetic medicine for HBC in Japan has yet to be established. To the best of our knowledge, the present study is the first to examine the frequency of use of genetic testing, RRM and RRSO in Japan. Furthermore, the type of genetic testing was mostly limited to *BRCA1/2* testing. Clinical practitioners may offer the appropriate testing corresponding to the medical history of patients and their family. The use of the multigene panel testing for HBC may be useful for patients who do not exhibit family history of various cancers other than HBC. Therefore, the current status of genetic services and the issues regarding HBC were investigated and it was identified that clinical cancer genetics requires further development in Japan.

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