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Satisfaction with Decision Regarding *BRCA1/2* Genetic Testing and Willingness to Undergo *BRCA1/2* Genetic Testing in the Future Among Breast Cancer Patients who Had not Previously Undergone *BRCA1/2* Genetic Testing in Japan

Mayuko INUZUKA^{*1,2)}, Takashi KUWAYAMA^{1,3)}, Terumasa SAWADA^{1,3)},
Sadako AKASHI-TANAKA^{1,3)} and Seigo NAKAMURA^{1,3)}

Abstract: Breast cancer patients must make their own decision of whether or not to undergo *BRCA1/2* genetic testing. The present study investigated satisfaction surrounding this decision and the willingness to undergo *BRCA1/2* genetic testing in the future among breast cancer patients who had not previously undergone *BRCA1/2* testing despite a family history of breast cancer. Consent was obtained from 103 eligible patients selected from breast cancer patients who had presented with suspected hereditary breast and ovarian cancer and attended genetic counseling sessions at our institution. Consenting patients were then asked to complete a survey by questionnaire. Irrespective of their decision to undergo *BRCA1/2* genetic testing, no patient reported being “not satisfied at all” or “not very satisfied”. Among the patients opting to not undergo *BRCA1/2* genetic testing, 64% responded that they would like to undergo *BRCA1/2* genetic testing in the future. Compared with the patients who did not want to undergo testing, those who wanted to undergo were more likely to harbor impressions that *BRCA1/2* genetic testing is “conducive to the selection of therapeutic modalities”, “helpful in deciding whether to undergo prophylactic surgery (oophorectomy, salpingectomy, and mastectomy)”, and “expensive”. Genetic counseling can improve satisfaction regarding the decision to undergo or not undergo *BRCA1/2* genetic testing. However, there were some patients who opted not to undergo testing, but they were willing to undergo *BRCA1/2* genetic testing in the future. Many of these patients might have found it cost-prohibitive to undergo testing immediately, despite realizing its benefits.

Key words: HBOC, *BRCA1/2* genetic testing, genetic counseling, decision-making

Introduction

Breast cancer is the most common cancer among Japanese women¹⁾. Hereditary carcinomas, the susceptibility of which is affected by mutations in a single gene, account for 5–10% of all breast cancers²⁾, with the most common being hereditary breast and ovarian cancer (HBOC).

¹⁾ Breast Surgical Oncology, Showa University Hospital, 1–5–8 Hatanodai, Shinagawa-ku, Tokyo 142–8666, Japan.

²⁾ Department of Genetic Counseling, Ochanomizu University.

³⁾ Department of Surgery, Division of Breast Surgical Oncology, Showa University School of Medicine.

* To whom corresponding should be addressed.

HBOC is an autosomal dominant disease caused by pathological mutations in either the *BRCA1* or *BRCA2* gene within germline cells inherited from parents to offspring at a probability of 1:2. By the age of 80 years, the reported incidence of breast cancer among individuals with *BRCA1* and *BRCA2* mutations is 72% and 69%, respectively, whereas that of ovarian cancer is 44% and 17%, respectively³⁾. Likewise, the reported occurrence rate of contralateral breast cancer within 20 years after a previous breast cancer diagnosis is 40% with *BRCA1* mutations and 26% with *BRCA2* mutations³⁾.

In the clinical setting, *BRCA1/2* genetic testing is highly beneficial in facilitating the selection of therapeutic modalities, early detection of associated lesions, prompt treatment, and in some cases, prophylactic interventions. The National Comprehensive Cancer Network Guidelines⁴⁾ recommend that genetic testing options be presented to individuals with suspected HBOC, as well as to their relatives; however, the choice to undergo such testing is entirely that of the patient. To aid patients in making informed decisions, medical personnel are obliged to provide genetic and other relevant information in prior genetic counseling sessions with a proper understanding of the needs, values, and expectations of the patients and their families. A systematic review of *BRCA1/2* genetic testing internationally revealed that 25%–96% of patients had undergone testing, with an average consultation rate of 59%⁵⁾. One study documented that the majority of women who had not previously undergone *BRCA1/2* genetic testing still opted to not undergo *BRCA1/2* genetic testing after listening to thorough explanations of the risks and benefits involved⁶⁾. Reasons cited for not choosing to undergo *BRCA1/2* genetic testing included patient perceiving the risk as low, doctor perceiving the risk as low, not a priority, insurance/work, and financial⁷⁾. Meanwhile, another study reported that women who had not previously undergone *BRCA1/2* genetic testing despite a family history of breast cancer were more prone to anxiety following genetic counseling than women who had tested positive for *BRCA1/2* mutations^{8,9)}.

The incidence of HBOC in Japan is believed to be largely comparable with that in the United States (US) and Europe^{10,11)}; however, although the awareness of hereditary breast cancer is gradually growing among the Japanese population, Japan lags far behind the US and European countries in terms of the social structures supporting genetic testing for familial breast cancers, including HBOC. Costs for *BRCA1/2* genetic testing and prophylactic surgery are also not covered by health insurance in Japan, and only a limited number of medical institutions are equipped to perform such tests and surgeries. Moreover, there is no legislation banning discrimination based on personal genetic information. Clarifying the impressions of patients on *BRCA1/2* genetic testing with no prior experience of genetic testing is crucial in planning future genetic therapeutic regimens, but no such attempt has been made.

The present study therefore aimed to investigate patients with no previous experience of *BRCA1/2* genetic testing despite having a family history of breast cancer to clarify whether 1) their satisfaction with decision making would differ from that of test takers, 2) they would consider *BRCA1/2* testing in the future, and/or 3) those who hoped for future testing would have impressions of *BRCA1/2* testing that differed from those of patients who did not plan for future testing.

Materials and methods

The patients in the present study were selected from individuals who met all of the following criteria: 1) those suspected of having HBOC based on a personal or familial medical history and who had attended genetic counseling sessions conducted by a specialized clinical geneticist or certified genetic counselor at our institution from October 2010 to August 2016; 2) women with breast cancer; 3) those who had one or more relatives with a family history of breast cancer within the third-degree relatives; 4) provided contact information when presenting at our institution for breast cancer treatment during this survey; 5) those who had no family member with confirmed *BRCA1/2* mutations; and, 6) those who had done no research including the process of undergoing *BRCA1/2* genetic testing.

The survey lasted from November 2014 to January 2017. The candidates were briefed regarding the objectives of the study by a specialized clinical geneticist or certified genetic counselor at least 2 months after their genetic counseling, and all participants provided written informed consent. Those who consented were asked to complete a questionnaire (Table 1) provided to them in the waiting room. After completion, the respondents returned their questionnaires to a receptionist at the institution. Following linkable anonymization, the collected questionnaires were securely stored. This study was approved by the Ethics Committee of Showa University School of Medicine.

Patient attributes and clinical information

Patients provided their age, marital status, employment status, and educational background at the time of the survey. Data on their child-bearing status, their age at the initial diagnosis of breast cancer, the presence of ovarian cancer, family history of cancer, date of the first genetic counseling session, and results of *BRCA1/2* genetic testing were collected from individual medical records.

*Satisfaction with decision making regarding *BRCA1/2* genetic testing*

The patients were asked to answer the question “How satisfied are you with your decision on whether to undergo *BRCA1/2* genetic testing?” on a five-point scale (1. Not satisfied at all, to 5. Extremely satisfied).

*Willingness to undergo *BRCA1/2* genetic testing in the future*

Only the patients who opted to not undergo *BRCA1/2* genetic testing were asked to answer the question “How willing are you to undergo *BRCA1/2* genetic testing in the future?” on a five-point scale (1. Not willing at all, to 5. Extremely willing). ”.

*Impressions of *BRCA1/2* genetic testing*

To assess the patients’ impressions of *BRCA1/2* genetic testing, we prepared a set of 11 relevant questions by referring to views and opinions expressed in previous studies on genetic

Table 1. Surveyed items or questions in the questionnaire

Part	Survey item or question	Answer for question
Patient attributes	Their age, marital status, employment status, educational background	
Satisfaction with decision-making regarding <i>BRCA1/2</i> genetic testing	How satisfied are you with your decision on whether to undergo <i>BRCA1/2</i> genetic testing?	<ol style="list-style-type: none"> 1. Not satisfied at all 2. Not very satisfied 3. Neither satisfied nor dissatisfied 4. Moderately satisfied 5. Extremely satisfied
Willingness to undergo <i>BRCA1/2</i> genetic testing in the future	How willing are you to undergo <i>BRCA1/2</i> genetic testing in the future?	<ol style="list-style-type: none"> 1. Not willing at all 2. Not very willing 3. Undecided 4. Moderately willing 5. Extremely willing
Impressions of <i>BRCA1/2</i> genetic testing	<p>Please answer your impression of <i>BRCA1/2</i> genetic testing.</p> <ul style="list-style-type: none"> • Helpful in ascertaining whether my breast/ovarian cancer is hereditary • Conducive to the selection of therapeutic modalities • Helpful in ascertaining the possibility of familial inheritance • Affects future examination • Helpful in deciding whether to undergo prophylactic surgery (oophorectomy, salpingectomy, and mastectomy) • Affects major life decisions (e.g., marriage, childbirth) • Causes tremendous stress to my family • Will not prevent me from worrying about breast/ovarian cancer • Expensive • May put me at a disadvantage in society • Will be a burden that affects my self-consciousness 	<ol style="list-style-type: none"> 1. Strongly disagree 2. Disagree 3. Neither agree nor disagree 4. Agree 5. Strongly agree

testing. The patients were asked to respond to each question on a five-point scale (1. Strongly disagree, to 5. Strongly agree). Prior to the start of the primary survey, a preliminary survey was conducted involving five women with breast cancer who had considered undergoing *BRCA1/2* genetic testing, and the phrasing of the main questions was adjusted based on their feedback. The reliability of the survey was ascertained using Cronbach's alpha coefficient ($\alpha = 0.64$). The validity of the survey was verified by a panel of experts comprising clinical geneticists specializing in hereditary breast cancer, surgeons specializing in breast surgery, nurses, and certified genetics counselors.

Statistical analysis

The collected data were analyzed using JMP Pro 13 software. Following descriptive statistics compilation, Fisher's exact test or Mann-Whitney U test was performed.

Results

Patient attributes and clinical information

A total of 597 women with breast cancer received genetic counseling at our institution during the period from October 2010 to August 2016. Of these, 103 met the eligibility criteria and expressed consent for enrollment in the study to a specialized clinical geneticist or genetic counselor during the survey period (97.2% rate of consent) (Figure 1). Median age of the participants at the time of initial breast cancer diagnosis was 44.0 years (25–67 years), and the median length of time from genetic counseling to the time of participation was 22.0 months (2–57 months). No patient had a previous history of ovarian cancer. *BRCA1/2* mutations were detected in 36 patients (35.0%), while 42 (40.8%) exhibited a variant of uncertain significance (VUS) or no mutation following *BRCA1/2* genetic testing, and 25 (24.3%) did not undergo any genetic testing. No statistically significant differences in patient attributes or clinical information were observed among these subgroups (Table 2).

*Satisfaction with decision making regarding *BRCA1/2* genetic testing*

The patients were divided into three groups to evaluate their decision-making satisfaction regarding *BRCA1/2* genetic testing: those with *BRCA1/2* mutations (Group 1); those with VUS or no mutation (Group 2); and, those that had opted not to undergo testing (Group 3) (Figure 2). Among all patients, 88.9% (32 out of 36) in Group 1, 97.6% (41 out of 42) in Group 2, and 64.0% (16 out of 25) in Group 3 responded that they were either “extremely satisfied” or “moderately satisfied” with their decision (Fisher’s exact test, $P < 0.01$). No patient in any group responded as “not satisfied at all” or “not very satisfied”.

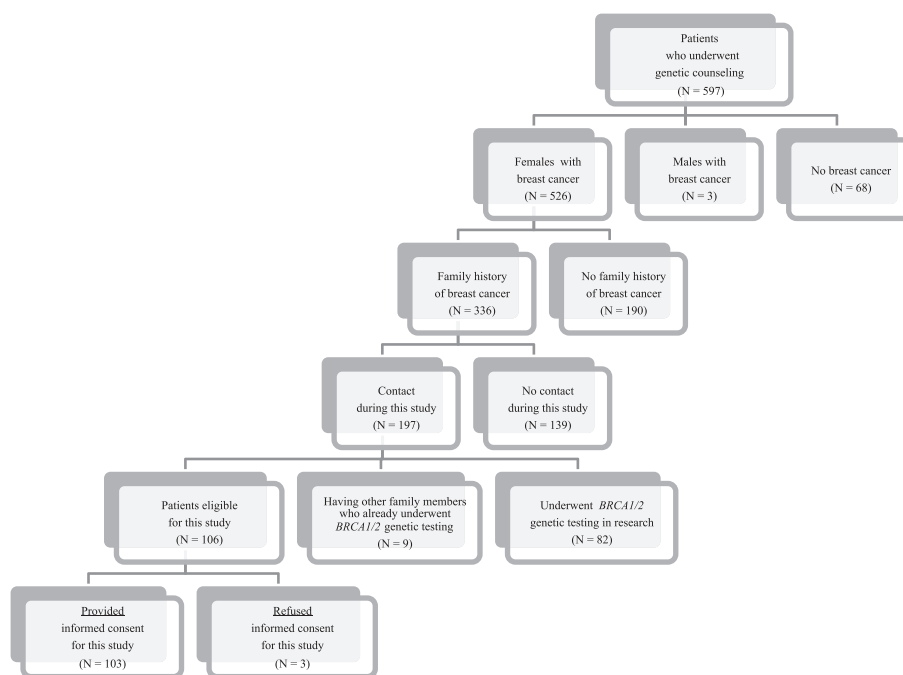


Fig. 1. Consort flow diagram illustrating the selection of eligible patients.

Table 2. Patient attributes and clinical information

Total Sample (N = 103)		Mutations detected (N = 36)		VUS or no mutations detected (N = 42)		No test performed (N = 25)		P-Value
		N	%	N	%	N	%	
Age	< 40 years	10	27.8	7	16.7	5	20.0	0.48
	≥ 40 years	26	72.2	35	83.3	20	80.0	
Marital status	Yes	23	63.9	31	73.8	19	76.0	0.58
	No	13	36.1	11	26.2	6	24.0	
Children	Yes	18	50.0	30	71.4	16	64.0	0.15
	No	18	50.0	12	28.6	9	36.0	
Employment	Full-time	17	47.2	14	33.3	12	48.0	0.35
	Part-time	5	13.9	9	21.4	3	12.0	
	Unemployed	14	38.9	15	35.7	10	40.0	
	Not specified	0	0.0	4	9.5	0	0.0	
Educational background	College or above	28	77.8	36	85.7	17	68.0	0.23
	High school or below	8	22.2	6	14.3	8	32.0	
Family history of ovarian cancer (within the third-degree relatives)	Yes	7	19.4	3	7.1	1	4.0	0.16
	No	29	80.6	39	92.9	24	96.0	
Age at the initial diagnosis of breast cancer	< 40 years	18	50.0	16	38.1	9	36.0	0.48
	≥ 40 years	18	50.0	26	61.9	16	64.0	
Length of time from genetic counseling to the time of participation	< 12 months	14	38.9	17	40.5	8	32.0	0.84
	≥ 12 months	22	61.1	25	59.5	17	68.0	

**p < .01, *p < .05, †p < .10 (Fisher's exact test)

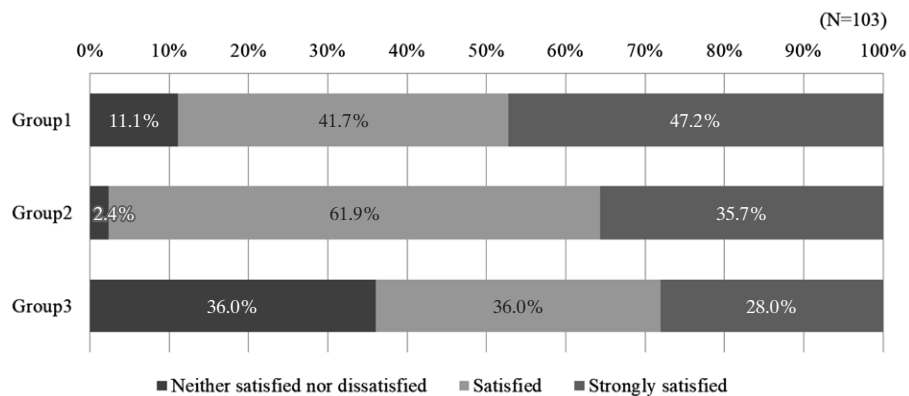


Fig. 2. Differences in the satisfaction of decision making regarding *BRCA1/2* genetic testing in Groups 1 (mutation detected), 2 (variant of uncertain significance or no mutation detected), and 3 (no test performed) (N = 103). Significance was evaluated using Fisher's exact test ($P < 0.01$). No patient replied "not satisfied at all" or "not very satisfied".

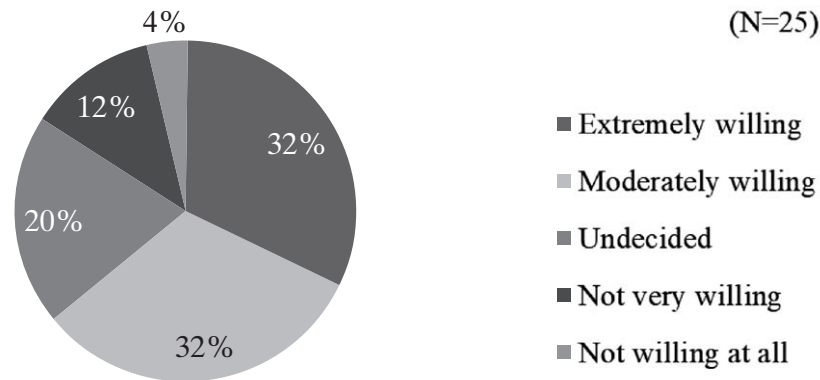


Fig. 3. Willingness to undergo *BRCA1/2* genetic testing in the future among the 25 patients in Group 3 (no test performed)

Willingness to undergo BRCA1/2 genetic testing in the future

The 25 patients in Group 3 were then asked how willing they were to undergo *BRCA1/2* genetic testing in the future. The responses “extremely willing” or “moderately willing”, “undecided”, and “not willing at all” or “not very willing” were received from 16 (64.0%), 5 (20.0%), and 4 (16.0%) patients, respectively (Figure 3).

Impressions of BRCA1/2 genetic testing

In accordance with their responses to the question discussed in the preceding section regarding future willingness to undergo *BRCA1/2* genetic testing, the Group 3 patients were further divided into two subgroups: those who responded that they were either “extremely willing” or “moderately willing” to undergo *BRCA1/2* genetic testing in the future (willing patients) and those who responded that they were either “undecided”, “not willing at all”, or “not very willing” to undergo a *BRCA1/2* genetic testing in the future (unwilling patients) (Table 3). The differences in impressions were compared between these subgroups. Compared with the unwilling patients, the willing patients were more likely to have stronger impressions that *BRCA1/2* genetic testing is “conducive to the selection of therapeutic modalities”, “helpful in deciding whether to undergo prophylactic surgery (oophorectomy, salpingectomy, and mastectomy)”, and “expensive” (Mann–Whitney U test, $P < 0.05$, respectively). Moreover, significantly more willing patients tended to think that *BRCA1/2* genetic testing is “helpful in ascertaining the possibility of familial inheritance” (Mann–Whitney U test, $P < 0.10$). No statistically significant difference was observed between the subgroups on any other questions posed (Table 3).

Discussion

The present study involved Japanese breast cancer patients who had not previously undergone *BRCA1/2* genetic testing despite having a family history of breast cancer. In these patients we ascertained, for the first time, their decision-making satisfaction regarding *BRCA1/2* genetic testing, their willingness to undergo *BRCA1/2* genetic testing in the future, and their impressions of *BRCA1/2* genetic testing attributes.

Table 3. Impressions of *BRCA1/2* genetic testing

Total Sample (N = 25)	Mean rank		P-value
	Unwilling	Willing	
Helpful in ascertaining whether my breast/ovarian cancer is hereditary	9.8	14.9	0.11
Conducive to the selection of therapeutic modalities	8.8	15.4	0.03*
Helpful in ascertaining the possibility of familial inheritance	9.3	15.1	0.06†
Affects future examination	10.9	14.2	0.30
Helpful in deciding whether to undergo prophylactic surgery (oophorectomy, salpingectomy, and mastectomy)	8.0	15.8	0.01*
Affects major life decisions (e.g., marriage, childbirth)	10.1	14.7	0.14
Causes tremendous stress to my family	12.8	13.1	0.93
Will not prevent me from worrying about breast/ovarian cancer	11.6	13.8	0.49
Expensive	8.1	15.8	0.01*
May put me at a disadvantage in society	13.5	12.7	0.80
Will be a burden that affects my self-consciousness	12.2	13.4	0.72

**p < .01, *p < .05, †p < .10 (Mann–Whitney U test)

Irrespective of their decision to undergo *BRCA1/2* genetic testing, no patient responded “not satisfied at all” or “not very satisfied”, suggesting that most patients reached a satisfactory conclusion after completely understanding the risks and benefits involved and after attending genetic counseling sessions, regardless of their decision to undergo testing. Nevertheless, compared with the patients who underwent testing, those who did not were generally less satisfied with their decision, with >30% responding that they were “neither satisfied nor dissatisfied”. Of the patients who had opted not to undergo testing, >60% hoped to undergo *BRCA1/2* genetic testing in the future. Compared with the patients who did not hope to undergo testing in the future, those who did were more likely to consider *BRCA1/2* genetic testing as “conducive to the selection of therapeutic modalities”, “helpful in deciding whether to undergo prophylactic surgery (oophorectomy, salpingectomy, and mastectomy)”, and “expensive”. Moreover, significantly more willing than unwilling patients tended to think that *BRCA1/2* genetic testing is “helpful in ascertaining the possibility of familial inheritance”. The results of the present study suggest that most patients who opted not to undergo testing, but were willing to undergo *BRCA1/2* genetic testing in the future, might have found it cost-prohibitive to undergo testing immediately despite realizing its benefits.

BRCA1/2 genetic testing can result in psychological burdens and social discrimination for patients and their families, thus it is important to respect a patient’s volition to not undergo testing. Conversely, the *BRCA1/2* status has become an index for selecting appropriate therapeutic modalities and improving postoperative survival. Clinically driven *BRCA1/2* genetic testing continues to increase in frequency annually, with attention being focused on the use of platinum preparations¹²⁾ and poly (ADP-ribose) polymerase inhibitors targeting carriers of *BRCA1/2* mutations¹³⁾. Additionally, in recent years, risk-reducing salpingo-oophorectomy and contralateral mastectomy have reduced the risks of ovarian/fallopian tube cancer¹⁴⁾ and breast cancer¹⁵⁾, respectively; however, these procedures have also improved the likelihood of postoperative survival¹⁶⁻¹⁹⁾.

Thus, supporting a patient's "right to know" has also increased in importance. The results of this study further demonstrated that genetic counseling might improve satisfaction regarding the decisions surrounding *BRCA1/2* genetic testing. Amid these circumstances, although genetic counseling preserves a patient's right to refuse testing, urgent measures must be taken in Japan beyond extending health insurance coverage of *BRCA1/2* genetic testing to supporting patients unable to undergo genetic testing due to financial reasons. According to reports, since genetic testing was covered by national health insurance in South Korea, there has been a decline in the number of patients who opted to not undergo genetic testing for financial reasons²⁰.

Additionally, in our study, it is noted that the patients who hoped to undergo *BRCA1/2* genetic testing in the future had the possibility of prophylactic surgery (oophorectomy, salpingectomy, and mastectomy) in mind. In addition to *BRCA1/2* genetic testing, efforts must be made in Japan to revise the health insurance scheme to cover prophylactic surgical options in cases of a positive diagnosis.

Limitations and future research

The primary limitation of the present study is the possible bias inherent in the collected samples. As the number of institutions equipped to perform *BRCA1/2* genetic testing is limited in Japan, this study collected data from only one institution. Moreover, the study involved only patients receiving ambulatory care for breast cancer and did not comprehensively investigate all participants in genetic counseling sessions. Another limitation is the small number of samples; an increase in sample size in future studies would allow the inclusion of more detailed patient attributes. Finally, the fact that all patients had a previous history of cancer is also a limitation. In Japan, it is exceptionally rare for a patient from a *BRCA*-positive family line to consider undergoing *BRCA1/2* genetic testing, and this quantitative study was unable to explore such patients. In future research, patients with no previous history of cancer should also be interviewed.

Conflict of interest disclosure

The authors have no conflicts of interest to declare.

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