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ORIGINAL ARTICLE

Factors affecting the implementation of cascade testing of patients with *BRCA1* or *BRCA2* pathogenic germline variants in Japan

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Abstract

In clinical management for hereditary cancer patients, risk assessment is needed not only for patients but also for their blood relatives. In people with Hereditary Breast and Ovarian Cancer syndrome (HBOC), benefits are demonstrated by identifying relatives with *BRCA1* and *BRCA2* pathogenic germline variants (PGV) and implementing clinical surveillance and risk-reduction surgeries for the at-risk organs. To date, the uptake of cascade testing has been reported to be insufficient, but only a limited number of studies have analyzed the barriers to cascade testing. The current study aimed to analyze the uptake of cascade testing in the relatives of Japanese HBOC probands and clarify the factors that promote cascade testing uptake. This retrospective study included 125 probands carrying *BRCA1* or *BRCA2* PGV and 425 of their first-degree relatives (FDRs). Individual clinicodemographic data were collected from medical records, and comparisons were made between those who did and did not undergo cascade testing. Ninety-two (21.6%) FDRs of HBOC probands underwent cascade testing. Approximately 70% of the relatives underwent testing within 6 months of the proband's genetic testing. Independent predictors of cascade testing of 425 FDRs were: being present at the proband's genetic counseling session [odds ratio (OR): 8.3, 95% CI 4.2–16.1], cost-free testing (OR: 2.4, 95% CI 1.4–4.2), being the child of a proband (OR: 1.9, 95% CI 1.1–3.2), and female sex (OR: 1.8, 95% CI 1.0–3.0). The cascade testing uptake rate of FDRs in this study was similar to or lower than other countries. cascade testing uptake can be improved in HBOC families by encouraging relatives (children, siblings, and parents) to attend genetic counseling with the proband. Further prospective studies are needed to pursue the reasons for accepting cascade testing, including an evaluation of intrafamily communication processes.

KEYWORDS
cascade testing, genetic counseling, HBOC, predictive factor

1 | INTRODUCTION

Hereditary Breast and Ovarian Cancer syndrome (HBOC) is one of the most common inherited cancer conditions (Momozawa et al., 2018). It is caused by *BRCA1* or *BRCA2* pathogenic germline variants (PGV), with an autosomal dominant inheritance form. In Japan, the germline testing of *BRCA1* and *BRCA2* genes has been covered by the national health insurance for the genetic diagnosis of HBOC and for the companion diagnostic for use of Poly (ADP-ribose) polymerase (PARP) inhibitors (Robson et al., 2017; Tutt et al., 2021) since 2020 (Hayashi et al., 2022). Today, the number of newly diagnosed cases of HBOC is increasing, at least partially due to the recent expansion and availability of cancer genome profiling tests (Minamoto et al., 2022).

In Japanese women with *BRCA1* or *BRCA2* PGV, the cumulative risks of breast cancer are 72.5% (*BRCA1*) and 58.3% (*BRCA2*), and those of ovarian cancer are 65.6% (*BRCA1*) and 14.8% (*BRCA2*) (Momozawa et al., 2022). Because these risks may be inherited by relatives, sequential genetic counseling and cascade testing are recommended for *BRCA1* or *BRCA2* PGV carriers (Samimi et al., 2017; Whitaker et al., 2021). In principle, cascade testing should be initiated with the proband's closest relatives and proceed outward to more distant relatives. Cascade testing can improves prognosis of *BRCA*1 or *BRCA2* PGV carriers with improved cost-effectiveness, by the combination of clinical surveillance and suitably timed risk-reduction surgeries (D'Andrea et al., 2015; Hadar et al., 2020; Xiao et al., 2019).

Various barriers have been reported to implementing cascade testing and affect both patients and medical providers. Patient-associated barriers include race, socioeconomic status, limitations of insurance coverage, relationships between the proband and family members, and low awareness of genetic risks. Medical provider-associated barriers include time constraints, privacy policies, and personnel shortages (Cheung et al., 2010; Srinivasan et al., 2020; Whitaker et al., 2021). For these reasons, the uptake of cascade testing has been reported at various rates; however, generally fewer than 30% in the eligible FDRs of hereditary cancer patients with proven PGVs (Ahsan et al., 2024; Lee et al., 2021; Whitaker et al., 2021). This study aimed to evaluate the uptake rate of cascade testing among FDRs of Japanese HBOC probands and to identify the demographic and clinical predictors associated with cascade testing uptake.

What is known about this topic

Various barriers have been reported to the implementation of cascade testing in families of Hereditary Breast and Ovarian Cancer syndrome (HBOC) patients, and uptake rates of cascade testing among first-degree relatives are reported to be 22%–60%. To date, factors such as being female, having children, having a daughter, and having a history of cancer have been listed as favorable predictors for cascade testing; however, few studies to date have focused on Japanese individuals.

What this paper adds to the topic

This study demonstrated that the cascade testing uptake rate among first-degree relatives of HBOC probands in Japan (21.6%) was similar to that reported in other Asian countries. Attendance at the proband's genetic counseling session was the most significant independent factor related to cascade testing uptake, although cost-free testing, being the child of the proband, and being female were also important. Attendance of family members at genetic counseling sessions aims to facilitate communication among family members and promote the understanding of HBOC and the importance of genetic testing.

2 | MATERIALS AND METHODS

2.1 | Participants

A medical record survey conducted at the Shizuoka Cancer Center, a hospital specializing in cancer medicine in Nagaizumi, Shizuoka Prefecture, a regional city in Japan, identified 125 HBOC probands who underwent genetic testing for germline *BRCA1* and *BRCA2* between June 2013 and September 2023 and their 512 FDRs. A "proband" was defined as an individual first identified as having a *BRCA1* or *BRCA2* PGV in their family. For this study, an FDR was defined as a person alive at the time of the initial genetic counseling session, aged 20 years or older, as the definition of adulthood in Japan has long been set as ≧20 years of age until 2022, and was able to provide informed consent. When one of the parents was already known to be a PGV carrier, or when three or more HBOC-related cancer patients were recognized within the parent's second-degree relatives, excluding the parent's descendants, the other parent was excluded from the current FDR definition. From the initial pool of prospective study subjects, 57 FDRs under the age of 20, 27 parents whose partners were known PGV carriers, and 3 FDRs with psychiatric conditions who are unable to provide informed consent were excluded from the analysis (Figure 1).

All probands and some of their FDRs underwent genetic counseling and testing at the Shizuoka Cancer Center Hospital. Encouragement of familial communication about cancer risk was included in the informed consent form for genetic testing and orally explained during pre- and post-test genetic counseling sessions. This recommendation was consistent across genetics providers. No letter or other resource was provided to families. If the relatives had no further contact with a geneticist or genetic counselor, no proactive steps were taken to facilitate communication among family members.

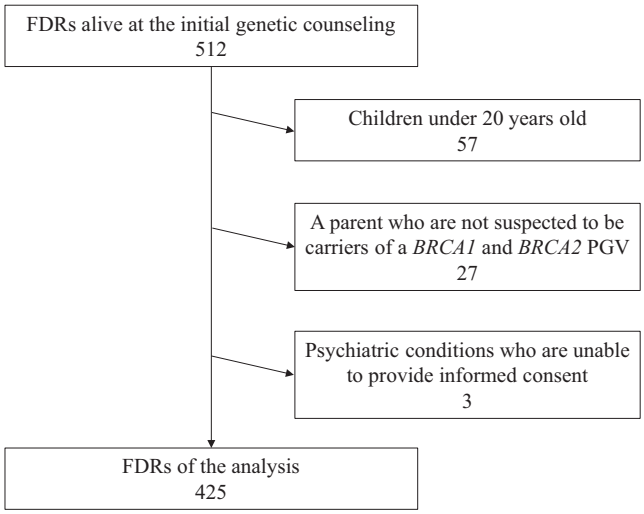

FIGURE 1 First-degree relatives under the age of 20, those with psychiatric conditions who are unable to provide informed consent, or who had a parent not suspected of being a carrier of a *BRCA1* or *BRCA2* PGV were excluded.

2.2 | Analyzed factors likely associated with cascade testing uptake

Clinical and demographic data for individuals who underwent genetic testing were collected from medical records. Information on family history of cancer and uptake of cascade testing in FDRs were collected based on reports from probands and relatives who underwent genetic counseling. For probands, data were collected on sex, age at the time of genetic testing, purpose for genetic testing, their number of children and siblings, type of cancer, PGV status, family members who attended genetic counseling, and family history of HBOC-related cancers (positive, if there was at least one HBOC-related cancer within their second-degree relatives). The purposes of genetic testing were divided into the following three categories: HBOC predisposition diagnosis, companion diagnosis for the indication of PARP inhibitors, and secondary findings of clinical genomic studies or comprehensive genomic profiling. Breast cancer, ovarian cancer, prostate cancer, and/or pancreatic cancer were defined as HBOC-related cancers.

For FDRs, data were collected on sex, their relationship to the proband, history of cancer diagnosis, number of children, and cost burden (cost-free test or charged test). For FDRs who underwent cascade testing, the period between the proband's testing and FDR's cascade testing was analyzed. Information on the FDRs who did not undergo cascade testing was collected from their relatives who attended genetic counseling sessions. Predictive factors associated with cascade testing updates were statistically analyzed among the above-noted factors using univariable and multivariable analyses.

2.3 | Statistical analysis

Several factors were compared between the FDRs who underwent cascade testing and those who did not. To determine predictors of genetic testing uptake in FDRs, Fisher's exact test (two-sided test) was used for the univariable analysis, and a logistic regression analysis was performed for the following multivariable analysis. A *p*-value equal to or less than 0.05 was considered statistically significant. Statistically significant and non-confounding factors analyzed in the univariable analysis were applied to the multivariable analysis. All statistical analyses were performed using JMP ver. 8 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Characteristics of the study population

The sociodemographic and clinical data of 125 probands are shown in Table 1. The median age of the probands at the time of genetic testing was 55 years. The purposes of their genetic testing were to diagnose HBOC (60 cases, 48.0%), as a companion diagnostic for PARP inhibitors (36 cases, 28.8%), and secondary findings from clinical genomic studies or comprehensive genome profiling (29 cases, 23.2%). A majority of probands were female (87.2%), had an HBOC-related cancer (90.4%), had a family history of HBOC-related cancers (70.4%), and had children (76.8%). At least one family member, including the spouse/partner, attended the proband's genetic counseling session for 72.0% of the HBOC probands (blood relatives accounted for 32.0%). Overall, 48 of 125 (38.4%) probands had one or more relatives who underwent cascade testing (Table 1).

Sociodemographic and clinical data of the 425 FDRs are summarized in Table 2. The FDRs included 196 (46.1%) females and 229 (53.9%) males, with a median age of 53 years. They had a cancer history in 16.5% of cases, and 62.8% had children. The FDR was a child of the proband in 33.6% of cases, a sibling in 48.0% of cases, and a parent in 18.4% of cases. Only 12.7% of FDRs attended a genetic counseling session with the proband (Table 2).

3.2 | Uptake of cascade testing

Forty-eight of 125 (38.4%) probands had one or more relatives who underwent cascade testing (Table 1). As Table 2 shows, among the FDRs, 92 (21.6%) of 425 underwent cascade testing. Ninety out of 92 FDRs underwent testing in our hospital, and for the remaining two FDRs, the results in other hospitals were obtained by the interview with probands. The median time between the proband's testing and the FDR's cascade testing was 91 days. Approximately 70% of the FDRs underwent cascade testing within 6 months of the proband's genetic testing, and more than 80% of the FDRs underwent cascade testing within 1 year (Figure 2).

3.3 | Factors associated with the uptake of cascade testing

Table 3 shows the results of univariable and multivariable analyses of the factors associated with cascade testing uptake rate among

TABLE 1 Demographics of HBOC probands ($n = 125$).

Demographics	Data
Age at time of *BRCA1* and *BRCA2* testing, median (range)	
Total	55.0 (26–85) y.o.
Female	54.0 (26–85) y.o.
Male	69.5 (45–76) y.o.
Sex, *n* (%)	
Female	109 (87.2%)
Male	16 (12.8%)
Purpose for genetic testing of *BRCA1* and *BRCA2*, *n* (%)	
Diagnosis of HBOC	60 (48.0%)
Companion diagnostics	36 (28.8%)
Secondary findings[a]	29 (23.2%)
Mutated gene, *n* (%)	
BRCA1	56 (44.8%)
BRCA2	68 (54.4%)
*BRCA1*and *BRCA2*	1 (0.8%)
Cancer history, *n* (%)	
HBOC-related[b]	113 (90.4%)
Non-HBOC-related	11 (8.8%)
Unaffected	1 (0.8%)
Family history of HBOC-raleted cancer[c], *n* (%)	
Yes	88 (70.4%)
No	37 (29.6%)
Existence of children, *n* (%)	
Yes	96 (76.8%)
No	29 (23.2%)
Existence of siblings, *n* (%)	
Yes	116 (92.8%)
No	9 (7.2%)
Family member attendance at genetic counseling, *n* (%)	
Yes	90 (72.0%)
No	35 (28.0%)
Blood relatives attendance at genetic counseling[d], *n* (%)	
Yes	40 (32.0%)
No	85 (68.0%)
One or more relatives underwent cascade testing, *n* (%)	
Yes	48 (38.4%)
No	77 (61.6%)

Abbreviations: HBOC, Hereditary Breast Ovarian Cancer syndrome; y.o., years old.

[a]Secondary findings from clinical genomic studies or comprehensive genome profiling testing.

[b]HBOC-related cancer: breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer.

[c]HBOC family history: at least one HBOC-related cancer within the second-degree relatives.

[d]Blood relatives who attended genetic counseling sessions, regardless of degree of consanguinity.

TABLE 2 Demographics of 425 first-degree relatives (FDRs) of 125 probands.

Demographics	Data
Age at cascade testing[a]	
Total	53.0 (20–96) y.o.
Female	53.0 (20–95) y.o.
Male	52.5 (20–96) y.o.
Sex, *n* (%)	
Female	196 (46.1%)
Male	229 (53.9%)
Cancer history, *n* (%)	
HBOC-related[b]	47 (11.1%)
Non-HBOC-related	23 (5.4%)
Unaffected	355 (83.5%)
Existence of children, *n* (%)	
Yes	267 (62.8%)
No	158 (37.2%)
Relationship to proband, *n* (%)	
Child	143 (33.6%)
Sibling	204 (48.0%)
Parent	78 (18.4%)
Attendance at genetic counseling sessions for proband, *n* (%)	
Attended	54 (12.7%)
Not attended	371 (87.3%)
Proceed with cascade testing, *n* (%)	
Yes	92 (21.6%)[c]
No	333 (78.6%)
Period since proband testing to cascade testing, median (range)	91 (13–1434) days

Abbreviation: y.o., years old.

[a]Information on the FDRs who did not undergo cascade testing was collected from the proband at the initial counseling.

[b]HBOC-related cancer: breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer.

[c]Female: 63/229 (27.5%), Male: 29/196 (14.8%).

FDRs. The following variables were significantly associated with the uptake of FDRs' cascade testing by univariable analysis; younger age (≦50 years) (34.7% vs. 11.1%, OR: 4.3, 95% CI: 2.6–7.1), female gender (27.5% vs. 14.8%, OR: 2.2, 95% CI: 1.3–3.6), cost-free testing (32.8% vs. 17.5%, OR: 2.3, 95% CI: 1.4–3.7), and attending the proband's genetic counseling session (64.8% vs. 15.4%, OR: 10.1, 95% CI: 5.4–19.0). Being a child of the proband showed a significantly higher uptake rate (33.6%) than other relationships (15.6%) (OR: 2.7, 95% CI: 1.7–4.4). The uptake rate of cascade testing was highest among probands' daughters (49.3%), followed by their sisters (17.4%), sons (16.2%), mothers (15.6%), fathers (15.2%), and brothers (13.7%). The multivariable analysis demonstrated that being female (OR: 1.8, 95% CI: 1.0–3.0), a proband's child (OR: 1.9, 95% CI:

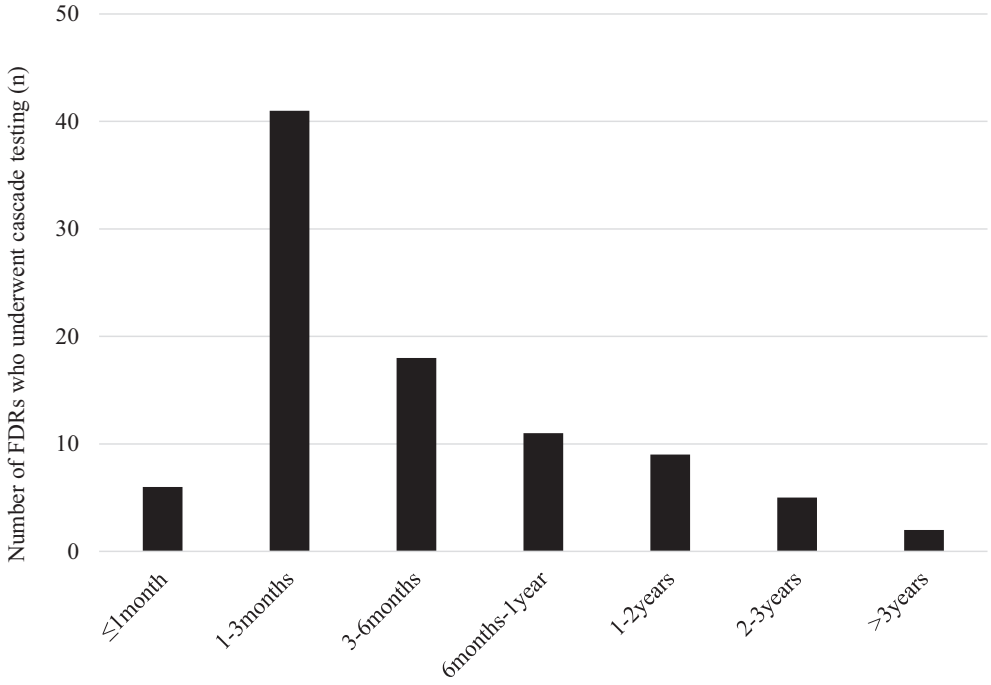

FIGURE 2 Timing of cascade testing among 425 FDRs. For FDRs who underwent cascade testing, the time period between the proband's testing and the cascade testing was tallied.

1.1–3.2), having access to cost-free testing (OR: 2.4 95% CI: 1.4–4.2), and being present at the proband's genetic counseling session (OR: 8.3, 95% CI: 4.2–16.1) were statistically independent predictors of cascade testing uptake in FDRs. The age category was excluded in the multivariable analysis, as it was strongly confounded with that of the relationship to the proband.

4 | DISCUSSION

To our knowledge, this is the first study to analyze the status of cascade testing uptake in HBOC families in Japan. Our results show that 21.6% of the FDRs of the probands in this study underwent testing (Table 2). Approximately 70% of the FDRs who underwent testing did so within 6 months of the proband's genetic testing (Figure 2). The strongest predictors of cascade testing uptake, analyzed by univariable analysis, were attending genetic counseling with the proband and being under the age of 50. Multivariable analyses revealed other independent predictors, including access to cost-free testing, female sex, and being a child of the HBOC proband.

The cascade testing uptake rate in this study was 21.6% (Table 2), which is similar to or lower than previous studies (Table 4) (Bodd et al., 2003; Finlay et al., 2008; Griffin et al., 2020; Holloway et al., 2008; Jeong et al., 2021; Julian-Reynier et al., 2000; Lee et al., 2021; Sanz et al., 2010; Trevisan et al., 2024). However, most studies were conducted single-centered; the recommended methods for cascade testing were not uniform. Furthermore, there were differences in study designs, such as information collection methods and genetic testing costs; hence a proper comparison cannot be made. In addition, genetic testing technology has advanced significantly over the past 20 years, and the cost of genetic testing has become significantly lower. To date, several factors, such as female sex, existence of children (especially daughters), and cancer history, have been reported as predictive factors of cascade testing (Table 4). The insufficient uptake rate of cascade testing in this study may be related to current Japanese lifestyle customs or the medical system, such as the reduced opportunities for information sharing due to the nuclear family structure or the national insurance system not covering cascade testing.

The strongest predictor of cascade testing was attendance at the proband's genetic counseling session. Perhaps the relatives receiving direct information from health professionals about the concept of HBOC and the importance of genetic testing may share this information among the family, and therefore lead to increasing acceptance of cascade testing. Meanwhile, of the 54 FDRs who participated in the proband's counseling, 19 (35.2%) did not undergo cascade testing (Table 3). Their reasons for refusal included being too old for future medical interventions, too young to begin surveillance, and/or having a mindset against genetic testing. Further research is needed to determine the effectiveness of genetic counseling, such as measuring relatives' understanding levels before and after genetic counseling.

In the current study, probands were encouraged by genetic health professionals to inform their relatives about their familial cancer risk, but the dissemination of information about this risk was left largely to the probands' discretion. Several studies have

TABLE 3 Factors associated with the uptake of cascade testing in 425 FDRs.

Analyzed factor	Uptake rate of cascade testing, *n*	Univariable analysis		Multivariable analysis[a]	
		OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age					
20–49 y.o.	34.7% (66/190)	4.3 (2.6–7.1)	<0.0001		
>50 y.o.	11.1% (26/235)				
Sex					
Female	27.5% (63/229)	2.2 (1.3–3.6)	0.002	1.8 (1.0–3.0)	0.042
Male	14.8% (29/196)				
Cancer history					
Yes	22.9% (16/70)	1.1 (0.6–2.0)	0.753		
No	21.4% (76/355)				
Family history of HBOC-raleted cancer excluding proband[b]					
Yes	21.9% (64/292)	1.1 (0.6–1.7)	0.899		
No	21.1% (28/133)				
Existence of children					
Yes	23.2% (62/267)	1.3 (0.8–2.1)	0.331		
No	19.0% (30/158)				
Relationship to proband					
Child	33.6% (48/143)	2.7 (1.7–4.4)	<0.0001	1.9 (1.1–3.2)	0.023
Other	15.6% (44/282)[c]				
Cost-free test					
Yes	32.8% (38/116)	2.3 (1.4–3.7)	0.001	2.4 (1.4–4.2)	0.002
No	17.5% (54/309)				
Attendance at genetic counseling sessions for the proband					
Attended	64.8% (35/54)	10.1 (5.4–19.0)	<0.0001	8.3 (4.2–16.1)	<0.0001
Not attended	15.4% (57/371)				
Total	21.6% (92/425)				

Abbreviations: CI, confidence interval; FDR, first-degree relative; OR, odd's ratio; y.o., years old.

[a]"Age" was excluded from the multivariable analysis because it was strongly confounded with "relationship to proband".

[b]Family history of HBOC-related cancer: at least one HBOC-related cancer within the second-degree relatives.

[c]Sibling: 15.7% (32/204), Parent: 15.4% (12/78).

shown that direct contact with relatives by telephone or letter from medical genetics professionals, rather than relying on the proband to provide information, has led to increased rates of cascade testing (Baroutsou et al., 2021; Frey et al., 2022). It follows based on this study that encouraging relatives to attend probands' genetic counseling sessions, with the proband's consent, would therefore increase the uptake in cascade testing by providing them with an opportunity to receive information directly from medical professionals. In addition, it may be worth considering that an annual small gathering and lectures with the patients and their families to promote their understanding of the concept of familial cancer syndromes, and emphasize the importance of familial communication for their health management.

The cascade testing uptake rate in this study was significantly higher among females (27.5% in females, 14.8% in males) (Table 3), which is thoroughly consistent with the data revealed in previous studies (Table 4). This is likely a reflection on the universal features of HBOC and its high penetrance cancers of the breast and ovary. Among the predictors of cascade testing uptake, cost-free testing had higher uptake, as expected, but conversely, 67.2% of FDRs did not undergo cascade testing, despite no cost burden (Table 3). This may be due to factors such as the relationship with the proband, living far away, or being busy with work or child-rearing. Even if cascade testing is provided free of charge, when the test results are positive, high-risk cancer screenings are not currently covered by the Japanese health insurance system if the individual does not have a history of breast or ovarian cancer. This may be another reason for relatives' refusal of testing. In the United Kingdom, the National Health Service (NHS) provides a breast screening program to all women aged 50–70 years

TABLE 4 Uptake rate of cascade testing in FDRs of HBOC probands in the previous literatures.

Author	Year	Country	HBOC probands, *n*	Uptake rate of BRT in FDRs			Predictors of high BRT uptake rate
				Female	Male	Total	
Julian-Reynier C	2000	France	37[a]	58% (61/106)	18% (12/67)	42% (73/173)	Female with cancer
Bodd TL	2003	Norway	75[a]	63% (53/84)	24% (21/88)	43% (74/172)	Female Male with a daughter
Finlay E	2008	The United States	115	70% (165/236)	44% (95/214)	58% (260/450)	Female Members of the maternal family
Holloway SM	2008	Scotland	54	58% (40/69)	8% (3/40)	39% (43/109)	Female Having children
Sanz J	2010	Spain	108	76% (167/219)	39% (71/180)	60% (238/399)	Female Highly educated Having children Previously diagnosed with cancer
Griffin NE	2020	The United States	29	57% (99/173)	28% (39/139)	44% (138/312)	Female
Lee DSC	2021	Malaysia	87	30% (70/236)	14% (32/237)	22% (102/473)	Sisters
Jeong GW	2021	Korea	392	41% (96/235)	18% (33/188)	31% (129/423)	Female Father is alive Daughter is alive
Trevisan L	2024	Italy	213	44% (252/568)	31.3% (83/265)	55.8% (169/303)	Female age < 30 years Paternal segregation of the pathogenic variants

Abbreviations: FDR, first-degree relative; HBOC, hereditary breast ovarian cancer.

[a]*BRCA1* mutation carriers only.

free of charge (French et al., 2020). This breast surveillance has been used by more than 70% of eligible women, and 42% of the resulting detected breast cancers were <15 mm in size (Breast Screening Programme, England, 2016–17). The NHS also provides women with *BRCA1* or *BRCA2* PGV screening via annual magnetic resonance imaging conducted between the ages of 30 and 50, and by mammography between ages 40 and 70. To encourage relatives to undergo genetic testing, improvements to Japan's medical system and an expansion of the national insurance coverage are necessary.

4.1 | Limitations

Our study has several limitations. It was conducted in a single hospital in Japan and based on retrospective data collection. Information on family history and cascade testing uptake were obtained by the interview with probands and their relatives, who attended our genetic counseling. During the counseling sessions, the probands were encouraged to share information about familial cancer risk with their relatives; however, the following update of relatives' information, including cascade testing results, was lacking. FDRs who did not receive cascade testing may not have been informed of the need by the proband. Further prospective studies are needed to evaluate intrafamily communication processes.

5 | CONCLUSION

In conclusion, the uptake rate of cascade testing in the FDRs of HBOC probands found in the current study is similar to or lower than the previous studies, but was insufficient to make definitive comparisons. Cascade testing uptake in HBOC pedigrees could be increased

by encouraging relatives to attend the proband's genetic counseling sessions and by promoting familial communication.

AUTHOR CONTRIBUTIONS

YK and HM wrote the manuscript. SN, NK, and HM gathered the clinical data. YK, YH, SH, EI, and RH gathered the data on genetic counseling. All authors reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no competing interests.

DATA AVAILABILITY STATEMENT

The data in this study are available from the corresponding author upon reasonable requests.

ETHICS STATEMENT

Human studies: The Institutional Review Board of the Shizuoka Cancer Center approved this study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Animal studies: No non-human animal studies were carried out by the authors for this article.

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