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Clinical utility of a self-administered questionnaire for assessment of hereditary gynecologic cancer

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Abstract

Background: A patient's medical history and familial cancer history are important information for assessing the risk of hereditary cancer. We have generated a self-administered questionnaire for patients with gynecologic cancer. This pilot study analyzed the usefulness of this questionnaire and the rates of patients that meet the Society of Gynecologic Oncology criteria in ovarian cancer and endometrial cancer patients.

Method: Ovarian or endometrial cancer patients were recruited for this study. After informed consent was obtained, participants completed the questionnaire. Genetic risks were assessed from the data of each patient's questionnaire by Society of Gynecologic Oncology guideline. Clinical and pathological findings were compared between the genetic risk groups.

Results: A total of 105 patients were identified with ovarian cancer and 56 patients with endometrial cancer eligible for this study. According to the Society of Gynecologic Oncology guideline, of the 105 ovarian cancer patients, 25 patients (23%) had a 20–25% risk and three patients (2.9%) had a 5–10% risk of hereditary breast and ovarian cancer syndrome. A further 22 patients (21%) had a 5–10% risk of Lynch syndrome. Two patients (1.9%) met the Amsterdam criteria II. Of 56 endometrial cancer patients, 24 patients (42.9%) had a 5–10% risk of Lynch syndrome. The endometrial cancer patients with genetic risk of Lynch syndrome were younger (mean age: 47.79) at diagnosis compared to patients without a genetic risk of Lynch syndrome (mean age: 57.91).

Conclusions: In this study, we were able to show that the newly designed questionnaire is a useful tool for evaluating cancer family history along with Society of Gynecologic Oncology criteria or Amsterdam criteria II. When considering the risk of Lynch syndrome for a patient with ovarian cancer, it is important to collect a second and third relative's family history.

Key words: family history, self-administered questionnaire, ovarian cancer, endometrial cancer, hereditary breast and ovarian cancer syndrome, Lynch syndrome

Introduction

Patients with gynecologic cancer have a risk of hereditary cancer syndrome. A patient with ovarian cancer, for instance, has a potential risk of hereditary breast and ovarian cancer syndrome (HBOC), Lynch syndrome and occasionally Peutz–Jeghers syndrome. A patient with endometrial cancer has a risk of Lynch syndrome and Cowden syndrome (1).

The clinical importance of diagnosing a patient or family members as having a hereditary cancer syndrome has been reported in many papers (2–4). For a patient with cancer, the results of genetic testing will affect the course of surgical treatment and chemotherapies (5,6). In addition, a patient diagnosed with a hereditary cancer syndrome will pay more attention to the risk of secondary cancer and can undergo cancer surveillance and take risk-reducing options. For an unaffected mutation carrier, a patient will also know her own risk of cancer and have the opportunity for cancer surveillance and risk-reducing therapies. Furthermore, family members will have the opportunity to take genetic counseling and genetic testing to know their risks of cancer.

A patient's medical history and familial cancer history are important information for assessing the risk of hereditary cancer syndrome. Young age, synchronous or metachronous cancer and family members with cancer on the same side of the family are factors suspicious for hereditary cancer syndrome. These patients are recommended to take genetic counseling and further genetic testing. Some criteria and guidelines show which patients should take further genetic counseling. The National Comprehensive Cancer Network (NCCN) guideline is one of the most popular guidelines for clinicians (7). Society of Gynecologic Oncology (SGO) and The American Congress of Obstetricians and Gynecologists (ACOG) guidelines for screening of HBOC or Lynch syndrome are also used by clinicians including gynecologists (2,8). The American Society of Clinical Oncology (ASCO) expert statement defined the minimum family history for patients with cancer as family history of cancer in first- and second-degree relatives. This statement recommended that age at cancer diagnosis, type of primary cancer and lineage (maternal or paternal side) should be recorded for each relative with cancer (4).

Despite the importance of cancer family history, clinicians including gynecologists do not always take an adequate cancer family history or assess the individual risk of hereditary cancer syndrome. Several studies have identified low rates of documentation of complete cancer family histories and low rates of referral to genetic counseling (9–12). A large study has shown that first- and second-degree family histories and age at cancer diagnosis were collected only in 29.1% of cancer patients, and only 43% of patients at risk for hereditary cancer were referred to genetic counseling (13). Therefore, a tool that can be easily used by clinicians and medical staff at gynecologic clinics for collecting a patient's medical history and familial cancer history may improve cancer family history taking and assessment in oncology practice.

We generated a self-administered questionnaire for collecting a patient's history and family history of cancer. It was designed to be beneficial for both physicians and patients to use, and covers hereditary cancer syndromes related to gynecologic cancers and the minimal family history for patients with cancer in the ASCO expert statement. This pilot study aimed to analyze the usefulness of this questionnaire and the rates of patients that meet the SGO criteria for ovarian cancer and endometrial cancer.

Materials and methods

Patients

Ovarian cancer or endometrial cancer patients were recruited to this study. Patients were outpatients or inpatients between April 2015 and December 2015 at the Department of Obstetrics and Gynecology, Keio University Hospital. Outpatients were previously diagnosed as ovarian cancer or endometrial cancer and regularly followed at our clinic. Inpatients were hospitalized for operation of ovarian cancer or endometrial cancer. The eligibility criteria were female gender, diagnosis of ovarian cancer or endometrial cancer, 20 years or older, Japanese-speaking and ability to provide informed consent.

Procedure

Potential participants among outpatients and inpatients were approached by doctors or medical staff. After informed consent was obtained, participants completed the family history of cancer questionnaire (Fig. 1) either during their waiting time for outpatient clinic or during the period they were admitted to the hospital as an inpatient. The information from these questionnaires was collected in our biobank database (Keio Women's Health Biobank) together with clinical and pathological data from the patients' medical records. Genetic risk for HBOC and Lynch syndrome were assessed from the data of each patient's questionnaire by SGO guideline with information other than the questionnaire blinded. This study was approved by the ethics committee of the School of Medicine, Keio University (approval number: 20070081).

Statistical analysis

Clinical and pathological findings were compared between the genetic risk groups; positive or negative. *T*-test, Pearson's chi-squared test and Fisher's exact test were conducted using SPSS. Any $P < 0.05$ was taken to indicate statistical significance.

Results

We identified 105 ovarian cancer patients and 56 endometrial cancer patients, including 15 multiple primary cancer patients as eligible for this study. The SGO guideline was applied to these patients. The SGO guideline provided criteria for physicians and medical staff to identify patients who may benefit from genetic risk assessment for HBOC and Lynch syndrome. According to the SGO guideline, each patient's risk for having an inherited predisposition to cancers as HBOC or Lynch syndrome was assessed as greater than 20–25% or 5–10% (8).

Of the 105 ovarian cancer patients, 25 patients (23%) met SGO 20–25% criteria and three patients (2.9%) met SGO 5–10% criteria for having a risk of HBOC. For the risk of Lynch syndrome, 22 patients (21%) met SGO 5–10% criteria. Two patients (1.9%) met the Amsterdam criteria II, clinical criteria which was created to identify patients who could be diagnosed as Lynch syndrome on the basis of patient and family history (14) (Table 1). Of 22 ovarian cancer patients having greater than 5–10% risk of Lynch syndrome, 14 patients (63.6%) met the criteria of 'patients with a first- or second-degree relative that meets the above criteria' (8) from the family history of cancer (Table 2). Of the 56 endometrial cancer patients, 24 patients (42.9%) met the SGO 5–10% criteria for having a risk of Lynch syndrome. One patient (1.8%) met the Amsterdam criteria II. Of the 24 endometrial cancer patients having greater than 5–10% risk of Lynch syndrome, seven patients (29.2%) met the criteria of 'patients with endometrial or colorectal cancer diagnosed prior to age 50' (8) and five patients (20.8%) met the criteria of 'patients with colorectal or endometrial cancer diagnosed at any age with two or more first- or second-degree relatives with Lynch/hereditary nonpolyposis colorectal cancer-associated tumors, regardless of age' (8) (Table 2). Of the 15 multiple primary cancer patients, eight patients

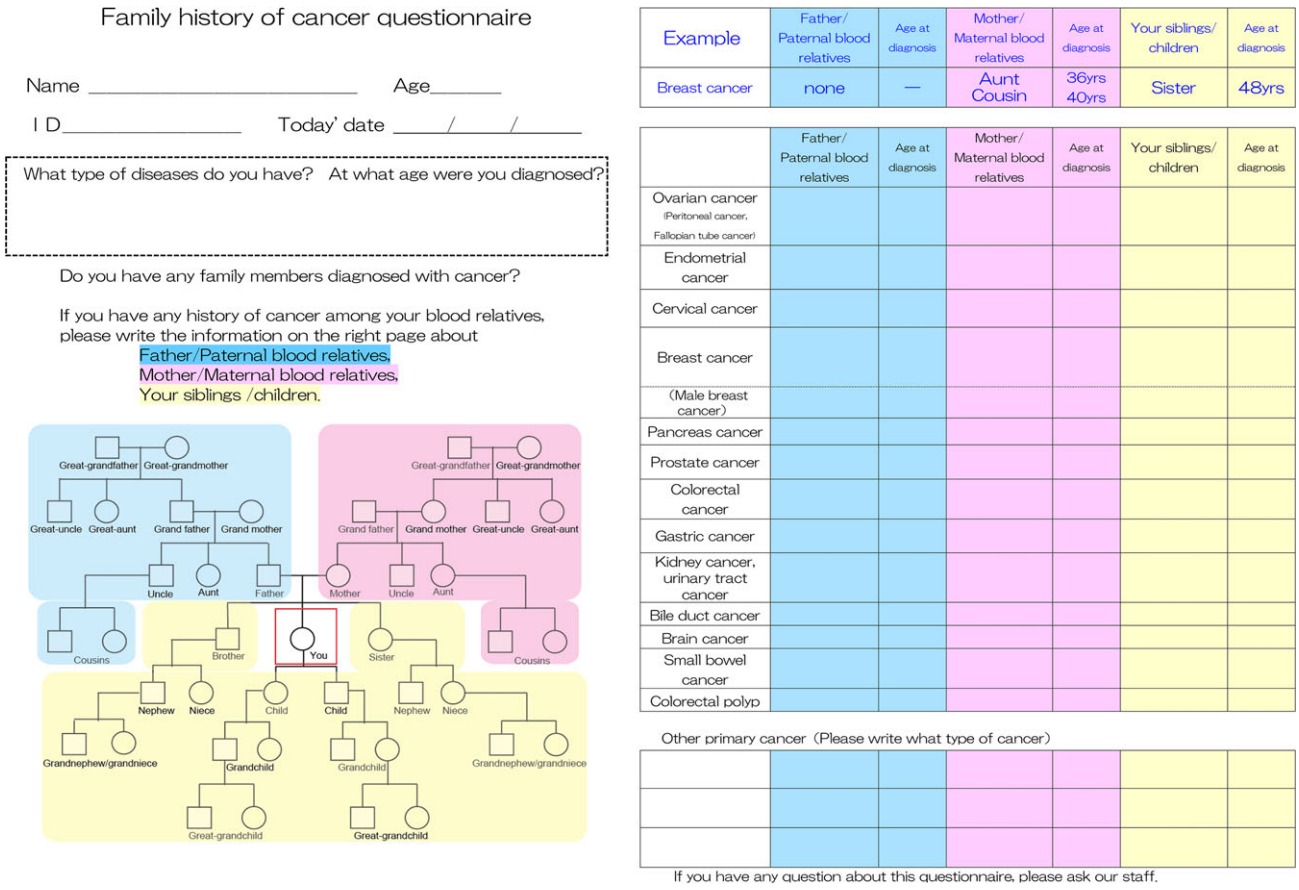


Figure 1. The self-administered questionnaire for collecting a patient's history and family history of cancer. This questionnaire can collect a personal medical history and family history including age at diagnosis, discriminate family histories between paternal or maternal side, and provides a diagram of a family tree to help patients understand the relationships between family members.

Table 1. Distribution of patients assessed of genetic risk by SGO guideline and Amsterdam criteria II for each cancer

	Ovarian cancer *n* (%)	Endometrial cancer *n* (%)	Multiple primary cancer *n* (%)
N	105	56	15
Genetic risk of HBOC			
20–25%	25 (23.8)	–	8 (53.3)
5–10%	3 (2.9)[a]	–	1 (6.7)
<5–10%	79 (75.2)	–	6 (40)
Genetic risk of Lynch syndrome			
5–10%	22 (21.0)	24 (42.9)	9 (60)
<5–10%	83 (79.0)	32 (57.1)	6 (40)
Amsterdam criteria II	2 (1.9)	1 (1.8)	0

SGO, Society of Gynecologic Oncology; HBOC, hereditary breast and ovarian cancer syndrome.

[a]Contains two patients who also met criteria of 20–25% risk of HBOC.

(53.3%) met SGO 20–25% for having a risk of HBOC and nine patients (60%) met SGO 5–10% criteria for having a risk of Lynch syndrome. The 15 multiple primary cancer patients comprised eight ovarian and endometrial cancer patients, five ovarian and breast cancer patients, one endometrial and breast cancer patient and one ovarian and endometrial and cervical cancer patient.

Table 3 compares the characteristics of 'Genetic risk of HBOC (+)' ovarian cancer patients who met SGO 20–25% or 5–10% criteria for having a risk of HBOC with those of 'Genetic risk of HBOC (−)' ovarian cancer patients who did not meet the criteria. There was no significant difference between the two groups in age at diagnosis, histology, stage at diagnosis and histological grade. Table 4 compares the characteristics of 'Genetic risk of Lynch syndrome (+)' ovarian cancer patients who met SGO 5–10% criteria for having a risk of Lynch syndrome with those of 'Genetic risk of Lynch syndrome (-)' ovarian cancer patients who did not meet the criteria. The patients with 'Genetic risk of Lynch syndrome (+)' tended to be younger (mean age 50.36 vs 55.78) at the time of diagnosis, but not significantly so ($p = 0.053$). Table 5 compares the characteristics of 'Genetic risk of Lynch syndrome (+)' endometrial cancer patients who met SGO 5–10% criteria for having a risk of Lynch syndrome with those of 'Genetic risk of Lynch syndrome (−)' endometrial cancer patients who did not meet the criteria. The patients in the 'Genetic risk of Lynch syndrome (+)' group were younger (mean age: 47.79) at diagnosis compared to 'Genetic risk of Lynch syndrome (−)' endometrial cancer patients (mean age: 57.91) ($P = 0.001$).

Figure 2 shows a family tree and questionnaire of a patient who met Amsterdam criteria II. The information on family history taken by the questionnaire was sufficient for the clinician and medical staff to assess whether the patient met Amsterdam criteria II.

Table 2. SGO criteria for patients with more than 5–10% risk of Lynch syndrome (the upper panel) and the criteria which patients met and the number of patients meeting the criteria (the lower panel)

SGO criteria for the patients with greater than 5–10% chance of having an inherited predisposition to endometrial, colorectal and related cancers. (Each criteria is named of alphabet for this study)

a. Patients with endometrial or colorectal cancer diagnosed prior to age 50

b. Patient with endometrial or ovarian cancer with a synchronous or metachronous colon or other Lynch/hereditary non-polyposis colorectal cancer (HNPCC)-associated tumor at any age

c. Patients with endometrial or colorectal cancer and a first degree relative with a Lynch/HNPCC-associated tumor diagnosed prior to age 50

d. Patients with colorectal or endometrial cancer diagnosed at any age with two or more first- or second-degree relatives with Lynch/HNPCC-associated tumors, regardless of age

e. Patients with a first- or second-degree relative that meets the above criteria

Alphabet of criteria which patients meet	No. of patients	Percent of total (%)
Ovarian cancer ($N = 22$)		
e	14	63.6
a, b	3	13.6
b, d	2	9.1
b/a, b, d, e/all	1 (each)	4.5 (each)
Endometrial cancer ($N = 24$)		
a	7	29.2
d	5	20.8
a, d	2	8.3
a, b	2	8.3
b	2	8.3
c/c, d, e/a, b, d, e/b, d, e/b, d/all	1 (each)	4.2 (each)

Table 3. Distribution of ovarian cancer patients categorized by genetic risk assessment of HBOC

	Genetic risk of HBOC (+) *n* (%)	Genetic risk of HBOC (−) *n* (%)	*P* value
N (=105)	26 (24.8%)	79 (75.2%)	
Age at diagnosis	53.96 ± 11.47	54.87 ± 11.84	0.732[a]
BMI	20.55 ± 2.74	20.75 ± 3.21	0.772[a]
Histology			
Clear	5 (19.2)	24 (30.4)	
Endometrioid	10 (38.5)	22 (27.8)	
Mucinous	3 (11.5)	7 (8.9)	
Serous	6 (23.1)	23 (29.1)	
Others	2 (7.7)	3 (3.8)	0.621[b]
Histology			
Serous	6 (23.1)	23 (29.1)	
Others	20 (76.9)	56 (70.9)	0.621[c]
Stage at diagnosis			
Stage 1–2	18 (69.2)	55 (69.6)	
Stage 3–4	8 (30.8)	24 (30.4)	1.00[c]
Grade			
Grade 1	9 (34.6)	16 (20.2)	
Grade 2	3 (11.5)	10 (12.7)	
Grade 3	8 (30.8)	16 (20.2)	
Grade NA	6 (23.1)	37 (46.8)	0.147[b]

BMI, body mass index.
[a]*t* test.
[b]Pearson's chi-square.
[c]Fisher's exact test.

Table 4. Distribution of ovarian cancer patients categorized by genetic risk assessment of Lynch syndrome

	Genetic risk of Lynch syndrome (+) *n* (%)	Genetic risk of Lynch syndrome (−) *n* (%)	*P* value
N (=105)	22 (21.0%)	83 (79.0%)	
Age at diagnosis	50.36 ± 13.06	55.78 ± 11.13	0.053[a]
BMI	20.81 ± 3.40	20.67 ± 3.02	0.846[a]
Histology			
Clear	5 (22.7)	24 (28.9)	
Endometrioid	10 (45.5)	22 (26.5)	
Mucinous	1 (4.5)	9 (10.8)	
Serous	4 (18.2)	25 (30.1)	
Others	2 (9.1)	3 (3.6)	0.287[b]
Histology			
Endometrioid	10 (45.5)	22 (26.5)	
Others	12 (54.5)	61 (73.5)	0.118[c]
Stage at diagnosis			
Stage 1–2	16 (72.7)	57 (68.7)	
Stage 3–4	6 (27.3)	26 (31.3)	0.799[c]
Grade			
Grade 1	8 (36.4)	17 (20.5)	
Grade 2	4 (18.2)	9 (10.8)	
Grade 3	2 (9.1)	22 (26.5)	
Grade NA	8 (36.4)	35 (42.2)	0.168[b]

[a]*t* test.
[b]Pearson's chi-square.
[c]Fisher's exact test.

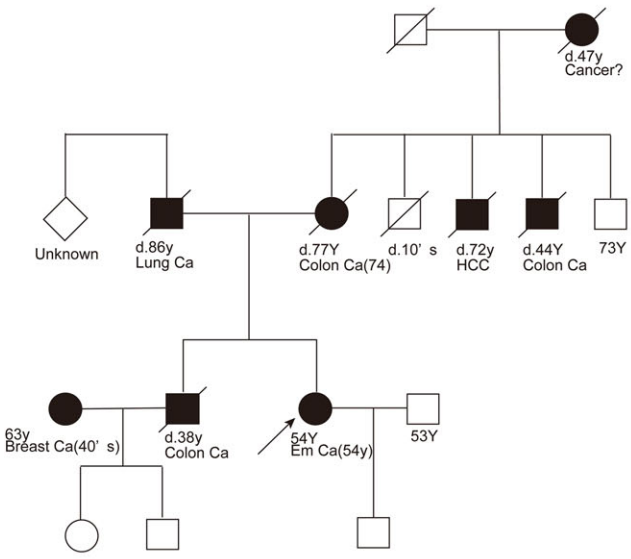
Table 5. Distribution of endometrial cancer patients categorized by genetic risk assessment of Lynch syndrome

	Genetic risk of Lynch syndrome (+) *n* (%)	Genetic risk of Lynch syndrome (−) *n* (%)	*P* value
N (=56)	24 (42.9%)	32 (57.1%)	
Age at diagnosis	47.79 ± 12.759	57.91 ± 8.364	0.001[a]
BMI	22.27 ± 5.10	22.71 ± 4.11	0.72[a]
Histology			
Endometrioid	21 (87.5)	26 (81.2)	
Others	3 (12.5)	6 (18.8)	0.402[b]
Stage at diagnosis			
Stage 1–2	21 (87.5)	29 (90.6)	
Stage 3–4	3 (12.5)	3 (9.4)	1[b]
Grade			
Grade 1	10 (41.7)	15 (46.9)	
Grade 2	8 (33.3)	9 (28.1)	
Grade 3	3 (12.5)	2 (6.3)	
Grade unknown	3 (12.5)	6 (18.7)	0.768[c]

[a]*t* test.
[b]Fisher's exact test.
[c]Pearson's chi-square.

Discussion

Evaluating a patient's risk of hereditary cancer syndrome is recommended for obstetricians and gynecologists, however, there are many difficulties in clinical practice. This self-administered questionnaire will be a useful tool for clinicians and medical staff to assess a patient's risk of hereditary cancer syndrome. This questionnaire can collect a personal medical history and family history including age



What type of diseases do you have? At what age were you diagnosed?

Endometrial cancer (54yrs)

	Father/ Paternal blood relatives	Age at diagnosis	Mother/ Maternal blood relatives	Age at diagnosis	Your siblings/ children	Age at diagnosis
Ovarian cancer (Peritoneal cancer, Fallopian tube cancer)						
Endometrial cancer						
Cervical cancer						
Breast cancer						
(Male breast cancer)						
Pancreas cancer						
Prostate cancer						
Colorectal cancer			Mother Uncle	74yrs 44yrs	Old brother	37yrs
Gastric cancer	Aunt	70yrs				
Kidney cancer, urinary tract cancer						
Bile duct cancer						
Brain cancer						
Small bowel cancer						
Colorectal polyp						

Figure 2. The family tree and questionnaire of a patient who met Amsterdam criteria II. The patient was diagnosed with endometrial cancer. She had two colorectal cancer patients as first relatives and one colorectal cancer patient as a second relative. Of those relatives, two patients were diagnosed at age <50 years.

at diagnosis, discriminate family histories between paternal or maternal side, and cover the minimal family history by following the ASCO expert statement (3). It also provides a diagram of a family tree to help patients understand the relationships between family members, and it is easy for clinicians to handle because it consists of only one page. In this pilot study, we were able to find two ovarian cancer patients and one endometrial cancer patient that met Amsterdam criteria II using only this questionnaire. This shows that the questionnaire is sufficient and useful for evaluating a cancer family history. We did not collect the time to complete this questionnaire, however, it was reported that the median time to complete another self-administered questionnaire, which consisted of five pages, was 17 min and an acceptable time (15).

In evaluating cancer family histories for ovarian cancer patients, there is a tendency to be more focused on diagnosing HBOC than Lynch syndrome (16). However, the present study found that 22 patients (21%) of ovarian cancer patients had a greater than 5–10% risk of Lynch syndrome by SGO criteria. Of those patients, 14 patients (63.6%) met the criterion of patient's first- or second relatives' medical history (criterion 'e' in Table 2) and 2 of 14 patients met the Amsterdam criteria II. This means that collecting a second and third relative's family history is important for assessing the risk of Lynch syndrome for ovarian cancer patients. For endometrial cancer patients, meanwhile, 29.2% met the criterion of young age (criterion 'a' in Table 2) and 20.8% met the criterion of family history among second-degree relatives (criterion 'd' in Table 2). Thus, endometrial cancer patients harboring a positive genetic risk of Lynch syndrome tend to be younger when following SGO criteria (Table 5).

In terms of detecting Lynch syndrome among endometrial cancer patients, the sensitivity of the SGO criteria is not high. Universal tumor testing, which is an approach to select patients with colorectal cancer for Lynch syndrome testing by immunohistochemistry of DNA mismatch repair (MMR) proteins, is also reported to be efficient for identifying Lynch syndrome among endometrial cancer patients (17,18). Universal tumor testing has the advantage of detecting Lynch syndrome in patients who are older and have less family history, who are hard to identify using clinical SGO criteria. It is also reported that the cost effectiveness of universal tumor testing is comparable. On the other hand, although universal testing is focused only on the identification of Lynch syndrome, multiple genes are reported to have susceptibilities to gynecologic cancers. In fact, among women who are not diagnosed as Lynch syndrome, a woman with a family history of endometrial cancer has an increased risk of endometrial cancer than a woman with no family history, suggesting that genes other than MMR gene would affect cancer susceptibility (19,20). Multigene testing used in clinical genetic testing would help us to find a cancer susceptible gene other than HBOC or Lynch syndrome. Collecting a cancer family history might provide important information to assess compatibility for multigene testing.

Should all gynecological cancer patients be assessed for cancer family history before considering genetic testing? The prevalence of *BRCA1/2* mutation is higher than 10% in ovarian serous carcinoma, and therefore it is reported that genetic testing should be considered even if an ovarian serous carcinoma patient has no family history of cancer (21,22). In our study, there was no significant difference of histology between the two groups harboring positive and negative HBOC risk in SGO criteria, but the prevalence of *BRCA1/2* mutation might be underestimated in serous ovarian cancer by SGO criteria. For non-serous ovarian cancer, the prevalence of *BRCA1/2* mutation is lower than 10%, and therefore evaluating a family history of cancer might be effective for genetic risk assessment (21).

This pilot study showed that the newly designed self-administered questionnaire is a useful tool for clinicians to evaluate gynecological

cancer patients for hereditary cancer risk. The accuracy of self-administered questionnaires has been reported in many papers, however, not the efficacy (15,23–25). We further need to evaluate the efficacy of this questionnaire by a prospective trial.

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Conflict of interest

Akira Hirasawa received a grant support and honorarium from AstraZeneca.

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