BRCA1/2 testing rates in epithelial ovarian cancer: a focus on the untested patients

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ABSTRACT

Background Since 2015, Dutch guidelines have recommended *BRCA1/2* pathogenic variant testing for all patients with epithelial ovarian cancer. Recently, recommendations shifted from germline testing to the tumor-first approach, in which tumor tissue is tested first, and subsequent germline testing is performed only in those with *BRCA1/2* tumor pathogenic variants or a positive family history. Data on testing rates and on characteristics of patients missing out on testing remain scarce.

Objective To evaluate *BRCA1/2* testing rates in patients with epithelial ovarian cancer and compare testing rates of germline testing (performed from 2015 until mid-2018) versus tumor-first testing (implemented mid-2018).

Methods A consecutive series of 250 patients diagnosed with epithelial ovarian cancer between 2016 and 2019 was included from the OncoLifeS data-biobank of the University Medical Center Groningen, the Netherlands. Testing rates were analyzed for the overall study population and for germline testing (period I) and tumor-first testing (period II) separately. Characteristics of tested and untested patients were compared and predictors for receiving testing were assessed with multivariable logistic regression.

Results Median age was 67.0 years (IQR 59.0–73.0) and 173 (69.2%) patients were diagnosed with high-grade serous carcinoma. Overall, 201 (80.4%) patients were tested. In period I, 137/171 (80.1%) patients were tested and in period II this was 64/79 (81.0%). Patients with non-high-grade serous carcinoma were significantly less likely to receive *BRCA1/2* testing than patients with high-grade serous carcinoma (OR=0.23, 95% CI 0.11 to 0.46, p<0.001).

Conclusions The results show that *BRCA1/2* testing rates are suboptimal and suggest that clinicians may not be choosing to test patients with epithelial ovarian cancer with non-high-grade serous ovarian carcinoma, although guidelines recommend *BRCA1/2* testing in all patients with epithelial ovarian cancer. Suboptimal testing rates limit optimization of care for patients with epithelial ovarian cancer and counseling of potentially affected relatives.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ *BRCA1/2* pathogenic variant testing provides valuable information on poly-(ADP-ribose)-polymerase inhibitor (PARP) inhibitor treatment options for patients with epithelial ovarian cancer and potential prevention in family members and is therefore recommended by Dutch guidelines for all patients with epithelial ovarian cancer.

WHAT THIS STUDY ADDS

⇒ *BRCA1/2* testing rates are suboptimal and our analysis showed that patients diagnosed with non-high-grade serous ovarian cancer are significantly less likely to receive testing than those with high-grade serous ovarian cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Patients who do not receive the recommended testing may miss out on optimal treatment, and their family members potentially miss out on genetic counseling and effective preventive measures.

INTRODUCTION

Ovarian cancer is the most lethal gynecological malignancy.[1] The lack of early symptoms and effective screening methods require alternative mitigation strategies to reduce its impact. Currently, detecting *BRCA1/2* pathogenic variants is considered a key component in epithelial ovarian cancer management for two main reasons. First, it provides opportunities for breast cancer prevention or surveillance in patients with a *BRCA1/2* germline pathogenic variant and for surveillance or risk-reducing prophylactic surgery in female relatives who are potentially at high lifetime risk of ovarian and breast cancer. Second, it identifies patients with *BRCA1/2* pathogenic variants in the germline or in tumor cells only, who will benefit greatly from poly-(ADP-ribose)-polymerase inhibitor (PARPi) therapy.[2–5]

Since 2015, *BRCA1/2* testing has been recommended by Dutch guidelines for all patients with epithelial ovarian cancer, regardless of age and histotype, and is covered by health insurances. Originally, this included counseling by clinical geneticists and then germline testing for all patients.[6] With reported improved outcomes in PARPi-treated women with *BRCA1/2* pathogenic variants, regardless of origin (germline or tumor), guidelines recently changed to recommend *BRCA1/2* tumor testing and subsequent germline testing only in those with tumor pathogenic variants or a positive family history.[7] This tumor-first approach reduces the number of patients being referred to clinical geneticists to only those with a *BRCA1/2* tumor pathogenic variant: approximately

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20% of all patients.[8 9] This lessens the burden for patients, decreases costs of genetic counseling and tests, and potentially reduces socioeconomic driven inequalities previously reported in genetic testing.[2 3]

Previous research has reported poor *BRCA1/2* testing rates,[4 5] and information on patients missing out on *BRCA1/2* testing remains scarce. However, insight into characteristics of untested patients may allow identification of barriers to testing, and thus can be of great value in addressing suboptimal testing. The purpose of this study was to evaluate *BRCA1/2* testing rates in patients with epithelial ovarian cancer diagnosed between January 2016 and December 2019 in the Netherlands, and to compare germline testing rates with the testing rates of the recently implemented tumor-first approach. Moreover, this study aimed to provide insight into characteristics of patients who were less likely to receive the recommended *BRCA1/2* testing.

METHODS

Participants and Data Collection

The University Medical Center Groningen is an academic, medical, tertiary referral center in the north of the Netherlands, covering an area with 3.4 million inhabitants. The medical center has been appointed an expertise center for familial breast and ovarian cancer by the European Reference Network.[10] The current study included patients from the OncoLifeS data-biobank, which is embedded within the structure of the University Medical Center Groningen to prospectively collect real-world data on clinical and lifestyle factors of patients with cancer.[11] The OncoLifeS data-biobank received approval by the medical center's medical ethical committee. All patients provide written informed consent to the OncoLifeS data-biobank before their data can be used.

Patients with epithelial ovarian cancer of adult age (≥18 years) were included in a consecutive series from January 2016 to December 2019. Patients with borderline ovarian tumors were not included. Data on patient demographics were collected from self-report questionnaires completed shortly after diagnosis. Collection of clinical data was embedded in routine care, and data on *BRCA1/2* tests were abstracted from patient files. Variable descriptions are included in Online supplemental box S1.

Data Definition

On July 1, 2018, *BRCA1/2* testing protocols in the University Medical Center Groningen changed from germline testing for all newly diagnosed patients with epithelial ovarian cancer to testing tumor tissue first, and subsequently referring only those with *BRCA1/2* tumor pathogenic variants or a positive family history to clinical geneticists for a germline test. To investigate testing rates for each testing guideline separately, patients were divided into two groups based on their date of diagnosis. July 1, 2018, was used as a cut-off date to split the study population into two groups, referred to as period I, including patients diagnosed before July 1, 2018, and period II, including patients diagnosed on or after July 1, 2018. Patients diagnosed at the end of period I were likely to receive testing in period II according to the tumor-first approach. However, this intermediate group was included in period I based on date of diagnosis.

Data Analysis

Patient and disease characteristics were described for the total study population and by period of diagnosis (period I and period II). Continuous variables were presented as median (IQR), and categorical variables as frequency (percentage). Groups were compared using the Mann-Whitney U test, X^2 test, or Fisher's exact test.

The primary outcome was the percentage of patients with epithelial ovarian cancer with a 'known *BRCA1/2* germline pathogenic variant status'—that is, those who completed the testing pathway. A patient's germline pathogenic variant status was considered known in two ways. First, a germline test can confirm the absence or presence of a *BRCA1/2* germline pathogenic variant. Second, a tumor test can confirm the absence of any *BRCA1/2* tumor pathogenic variants, which indicates the absence of germline pathogenic variants. In the case of a tumor pathogenic variant, a germline test is required to analyze whether the pathogenic variant is of germline or somatic origin. Patients with a known *BRCA1/2* germline pathogenic variant status will hereafter be referred to as 'tested' and those with an unknown *BRCA1/2* germline pathogenic variant status as 'untested'.

The primary outcome was analyzed for the total study population and by period of diagnosis (period I and period II). Patient and disease characteristics were also summarized by testing status: tested versus untested patients, and these groups were compared using the Mann-Whitney U test, X^2 test or Fisher's exact test. Furthermore, patient and disease characteristics of tested and untested patients were compared by period of diagnosis (period I and period II), to investigate if potential differences existed for both the germline testing guideline (period I) and the tumor-first testing guideline (period II). Multivariable logistic regression analysis was performed to evaluate histotype, age at diagnosis, and period of diagnosis as predictors of receiving *BRCA1/2* testing. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 23 (IBM) and two-sided p values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

A total of 250 newly diagnosed patients with epithelial ovarian cancer were included, 171 patients diagnosed in period I and 79 patients diagnosed in period II (Table 1). Median age of all patients was 67.0 years (59.0–73.0). Most patients were diagnosed with high-grade serous carcinoma (n=173, 69.2%) and diagnosed in International Federation of Gynecology and Obstetrics (FIGO) stage III (n=132, 52.8%). The proportion of patients with a low educational level was significantly greater in period I than in period II (period I: n=56, 32.7%; period II: n=14, 17.7%; p=0.049). Other characteristics did not significantly differ between period I and period II.

BRCA1/2 Testing Rates and Test Outcomes

Of all 250 patients, 201 (80.4%) patients were tested (Table 2). A total of 63.6% of all patients were tested within 1 year after diagnosis (Online supplemental table S1). Of the patients diagnosed in period I, 80.1% was tested, and in period II this was 81.0% (Table 2), showing similar figures in both periods. For three patients (1.2%) the tumor test was unsuccessful and

Table 1 Patient and disease characteristics at baseline for all patients and by time of diagnosis (period I and period II)

	All patients		Patients diagnosed in period I*		Patients diagnosed in period II*		
	n=250		n=171		n=79		
Characteristics	***N***	**%**	***N***	**%**	***N***	**%**	**P value**
Age at diagnosis, median (IQR)	67.0 (59.0–73.0)		67.0 (59.0–72.0)		66.0 (59.0–73.0)		0.973
BMI at diagnosis, kg/m^2							0.298
<18.5	8	3.2	3	1.8	5	6.3	
≥18.5 and ≤24.9	108	43.2	77	45.0	31	39.2	
≥25.0 and ≤29.9	81	32.4	53	31.0	28	35.4	
≥30	46	18.4	32	18.7	14	17.7	
Unknown	7	2.8	6	3.5	1	1.3	
Country of birth (self-reported)							0.877
The Netherlands	192	76.8	133	77.8	59	74.7	
Other	7	2.8	5	2.9	2	2.5	
Unknown	51	20.4	33	19.3	18	22.8	
Educational level† (self-reported)							0.049
Low	70	28.0	56	32.7	14	17.7	
Medium	109	43.6	67	39.2	42	53.2	
High	6	2.4	5	2.9	1	1.3	
Unknown	65	26.0	43	25.1	22	27.8	
Parity at diagnosis (self-reported)							0.595
Yes	157	62.8	111	64.9	46	58.2	
No	40	16.0	26	15.2	14	17.7	
Unknown	53	21.2	34	19.9	19	24.1	
Smoking status at diagnosis (self-reported)							0.983
Never smoker	100	40.0	69	40.4	31	39.2	
Former smoker	86	34.4	58	33.9	28	35.4	
Current smoker	21	8.4	15	8.8	6	7.6	
Unknown	43	17.2	29	17.0	14	17.7	
Family history of cancer at diagnosis (self-reported)							0.914
Yes	139	55.6	96	56.1	43	54.4	
No	67	26.8	46	26.9	21	26.6	
Unknown	44	17.6	29	17.0	15	19.0	
WHO performance status at diagnosis							0.478
0	142	56.8	97	56.7	45	57.0	
1	54	21.6	36	21.1	18	22.8	
2	14	5.6	7	4.1	7	8.9	
3	3	1.2	3	1.8	–	–	
Unknown	37	14.8	28	16.4	9	11.4	
Frailty at diagnosis (GFI)							0.890
<4 (non-frail)	114	45.6	76	44.4	38	48.1	
≥4 (frail)	47	18.8	33	19.3	14	17.7	
Unknown	89	35.6	62	36.3	27	34.2	
Histology at diagnosis							0.352
High-grade serous	173	69.2	121	70.8	52	65.8	
Low-grade serous	8	3.2	6	3.5	2	2.5	
Mucinous	11	4.4	7	4.1	4	5.1	

Continued

Table 1 Continued

Characteristics	All patients n=250		Patients diagnosed in period I* n=171		Patients diagnosed in period II* n=79		P value
	N	%	*N*	%	*N*	%	
Endometrioid	26	10.4	17	9.9	9	11.4	
Clear cell	23	9.2	14	8.2	9	11.4	
Carcinosarcoma	4	1.6	1	0.6	3	3.8	
Adenocarcinoma NOS	5	2.0	5	2.9	–	–	
FIGO stage at diagnosis							0.976
I	40	16.0	28	16.4	12	15.2	
II	24	9.6	17	9.9	7	8.9	
III	132	52.8	88	51.5	44	55.7	
IV	53	21.2	37	21.6	16	20.3	
Unknown	1	0.4	1	0.6	–	–	

*Period I: January 1, 2016 until July 1, 2018. Period II: July 1, 2018 until January 1, 2020.
†Educational levels were defined as follows: low=primary or secondary education or less; medium=vocational education; high=university or higher education.
BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; GFI, Groningen Frailty Index; IQR, Interquartile range; NOS, not otherwise specified.

there was no test result available. These three patients were not referred for germline testing for unknown reasons and their *BRCA1/2* germline pathogenic variant status remains unidentified. One patient (0.4%) had a *BRCA1* tumor pathogenic variant but decided not to proceed with genetic counseling. Therefore, this patient was omitted from further analyses.

In period I, most patients received a germline test only (n=93, 54.4%). In period II, the proportion of patients receiving a germline

Table 2 *BRCA1/2* testing rates for all patients and by period of diagnosis (period I and period II)

	All patients n=250		Patients diagnosed in period I* n=171		Patients diagnosed in period II* n=79		P value
	N	%	*N*	%	*N*	%	
Tested: known germline pathogenic variant status	201	80.4	137	80.1	64	81.0	1.000
Untested: unknown germline pathogenic variant status	49	19.6	34	19.9	15	19.0	
No test offered	45	18.0	33	19.3	12	15.2	
Unsuccessful tumor test†	3	1.2	–	–	3	3.8	
Rejected germline test‡	1	0.4	1	0.6	–	–	
Test scenarios							<0.001
No test or inconclusive test result	48	19.2	33	19.3	15	19.0	
Germline test only	97	38.8	93	54.4	4	5.1	
Tumor test only§	61	24.4	20	11.7	41	51.9	
Tumor+germline test	44	17.6	25¶	14.6	19	24.1	

*Period I: January 1, 2016, until July 1, 2018. Period II: July 1, 2018, until January 1, 2020.
†Unsuccessful tumor test and no subsequent referral for germline test.
‡Patient withdrew from germline testing after tumor pathogenic variant was detected.
§All tumor tests were performed after July 1, 2018.
¶25 patients diagnosed in period I received both a tumor and germline test. The tumor tests were performed after a conclusive germline test indicated the absence of a germline pathogenic variant, to potentially detect a tumor pathogenic variant.

Table 3 *BRCA1/2* test results for all tested patients and by period of diagnosis (period I and period II)

	All tested patients		Tested patients diagnosed in period I*		Tested patients diagnosed in period II*		
	n=201		n=137		n=64		
	N	%	*N*	%	*N*	%	P value
No GPV	186	92.5	126	92.0	60	93.8	
BRCA1/2 GPVs detected	15	7.5	11	8.0	4	6.3	0.269
BRCA1 GPV	10	5.0	6	4.4	4	6.3	
BRCA2 GPV	5	2.5	5	3.6	–	–	
Somatic *BRCA1/2* PVs detected	9	4.5	4†	2.9	5	7.8	
Somatic *BRCA1* PV	6	3.0	4	2.9	2	3.1	
Somatic *BRCA2* PV	3	1.5	–	–	3	4.7	

*Period I: January 1, 2016, until July 1, 2018. Period II: July 1, 2018, until January 1, 2020.
†Tumor tests were performed after July 1, 2018.
GPV, germline pathogenic variant; PV, pathogenic variant.

test only decreased to 5.1% and most patients received a tumor test only (51.9%). The overall proportion of patients receiving a germline test decreased from 69.0% in period I (germline test only: 54.4%; tumor+germline test: 14.6%) to 29.2% in period II (germline test only: 5.1%; tumor+germline test: 24.1%).

BRCA1 pathogenic variants were detected in 8.0% of the tested patients (n=16), including 10 germline pathogenic variants (5.0%), and *BRCA2* pathogenic variants were detected in 4.0% of the tested patients (n=8), including five germline pathogenic variants (2.5%) (Table 3). In period I, *BRCA1/2* germline pathogenic variants were detected in 8.0% (n=11) of the tested patients and in period II this was 6.3% (n=4). In period II, somatic *BRCA1/2* pathogenic variants were detected in an additional 7.8% of the tested patients with no germline pathogenic variants (n=5). There were no statistically significant differences in *BRCA1/2* germline pathogenic variants detected in period I vs period II. All *BRCA1/2* pathogenic variants were detected in patients with high-grade serous carcinoma (Online supplemental table S2).

Comparing Characteristics by Testing Status

Tested patients were relatively younger than untested patients (median age: 66.0 years (59.0–72.0) vs 70.0 years (61.3–75.0), p=0.023: Table 4). Furthermore, testing rates were significantly higher in patients with high-grade serous carcinoma than in patients with non-high-grade serous carcinoma (n=150, 74.6%; n=48, 23.9%, respectively; p<0.001). Also, testing rates were significantly higher in patients diagnosed with an advanced FIGO stage (III/IV), as compared with testing rates of patients with an early FIGO stage (I/II) (n=155, 77.1%; n=45, 22.4%, respectively; p=0.018).

Characteristics of tested and untested patients were compared per period of diagnosis to investigate whether the group differences existed regardless of the active guideline (Table 5). Untested patients were significantly older than tested patients in period I (median age: 70.0 years (66.0–75.0) vs 66.0 years (58.0–72.0), p=0.009). In period II, the median age of untested and tested patients was similar (untested: 65.0 years (56.0–78.0); tested: 66.0 years (59.0–72.0)). In both periods, testing rates were significantly higher in patients with high-grade serous carcinoma than in those with non-high-grade serous carcinoma (period I: n=103, 75.2%; n=31, 22.6%, respectively; p=0.019; period II: n=47, 73.4%; n=17, 26.6%, respectively; p=0.006).

Multivariable Regression Analysis

In multivariable regression analysis adjusted for period of diagnosis and histotype, increasing age was significantly associated with lower chances of receiving *BRCA1/2* testing (OR=0.96, 95% CI 0.93 to 0.99, p=0.012; Online supplemental table S3). Furthermore, patients diagnosed with non-high-grade serous carcinoma were significantly less likely to receive *BRCA1/2* testing than patients with high-grade serous carcinoma (OR=0.23, 95% CI 0.11 to 0.46, p<0.001, adjusted for age at diagnosis and period of diagnosis).

DISCUSSION

Summary of Main Results

In the current study, 80.4% of all patients received *BRCA1/2* testing. The proportion of tested patients was similar for period I and II: 80.1% and 81.0%, respectively. Overall, older patients and patients with non-high-grade serous carcinoma were less likely to receive testing. Also, patients diagnosed at an early stage (FIGO I/II) were less frequently tested, which is likely to be a result of the greater proportion of non-high-grade serous carcinoma in this group.

Results in the Context of Published Literature

Overall, *BRCA1/2* pathogenic variants were detected in 12.0% of all tested patients, which is relatively low compared with the prevalence of 16–19% reported by others.[8 9] This lower percentage could partly be explained by an active performance of risk-reducing salpingo-oophorectomies in our region. The percentage of *BRCA1/2* germline pathogenic variant carriers undergoing risk-reducing salpingo-oophorectomies increased from 81% to 95% in our medical center after stopping ovarian cancer screening in 2009, and unpublished data from our hospital indicate that this now reaches 99%.[12] With more *BRCA1/2* germline pathogenic variant carriers opting for risk-reducing salpingo-oophorectomies, the proportion of women with *BRCA1/2* germline pathogenic variants among newly diagnosed patients is likely to be smaller.

Table 4 Patient and disease characteristics at baseline for all patients and by testing status (tested and untested)

Characteristics	All patients n=250		Tested n=201		Untested n=48		P value
	N	%	*N*	%	*N*	%	
Age at diagnosis, median (IQR)	67.0 (59.0–73.0)		66.0 (59.0–72.0)		70.0 (61.3–75.0)		0.023
Year of diagnosis							0.497
2016	48	19.2	36	17.9	12	25.0	
2017	80	32.0	64	31.8	15	31.3	
2018	71	28.4	61	30.3	10	20.8	
2019	51	20.4	40	19.9	11	22.9	
BMI at diagnosis, kg/m^2							0.534
<18.5	8	3.2	5	2.5	3	6.3	
≥18.5 and ≤24.9	108	43.2	86	42.8	21	43.8	
≥25.0 and ≤29.9	81	32.4	65	32.3	16	33.3	
≥30	46	18.4	38	18.9	8	16.7	
Unknown	7	2.8	7	3.5	–	–	
Country of birth (self-reported)							0.770
The Netherlands	192	76.8	154	76.6	38	79.2	
Other	7	2.8	6	3.0	–	–	
Unknown	51	20.4	41	20.4	10	20.8	
Educational level* (self-reported)							0.399
Low	70	28.0	53	26.4	16	33.3	
Medium	109	43.6	92	45.8	17	35.4	
High	6	2.4	4	2.0	2	4.2	
Unknown	65	26.0	52	25.9	13	27.1	
Parity at diagnosis (self-reported)							0.164
Yes	157	62.8	131	65.2	26	54.2	
No	40	16.0	28	13.9	12	25.0	
Unknown	53	21.2	42	20.9	10	20.8	
Smoking status Former smoker row 70 Tested, 15 Not tested but Total = 86 diagnosis (self-reported)							0.882
Never smoker	100	40.0	79	39.3	21	43.8	
Former smoker	86	34.4	70	34.8	15	31.3	
Current smoker	21	8.4	18	9.0	3	6.3	
Unknown	43	17.2	34	16.9	9	18.8	
Family history of cancer at diagnosis (self-reported)							0.485
Yes	139	55.6	115	57.2	23	47.9	
No	67	26.8	52	25.9	15	31.3	
Unknown	44	17.6	34	16.9	10	20.8	
WHO performance status at diagnosis							0.217
0	142	56.8	113	56.2	29	60.4	
1	54	21.6	43	21.4	11	22.9	
2	14	5.6	11	5.5	3	6.3	
3	3	1.2	1	0.5	2	4.2	
Unknown	37	14.8	33	16.4	3	6.3	
Frailty at diagnosis (GFI)							0.533
<4 (non-frail)	114	45.6	91	45.3	23	47.9	
≥4 (frail)	47	18.8	36	17.9	11	22.9	

Continued

Table 4 Continued

Characteristics	All patients n=250		Tested n=201		Untested n=48		P value
	N	%	*N*	%	*N*	%	
Unknown	89	35.6	74	36.8	14	29.2	
Histology at diagnosis							<0.001
High-grade serous	173	69.2	150	74.6	22	45.8	
Non-high-grade serous	72	28.8	48	23.9	24	50.0	
Adenocarcinoma NOS	5	2.0	3	1.5	2	4.2	
FIGO stage at diagnosis							0.018
I/II	64	25.6	45	22.4	19	39.6	
III/IV	185	74.0	155	77.1	29	60.4	
Unknown	1	0.4	1	0.5	–	–	

One patient who rejected germline test was not included in analysis by testing status.
*Educational levels were defined as follows: low=primary or secondary education or less, medium=vocational education, high=university or higher education.
BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; GFI, Groningen Frailty Index; IQR, Interquartile range; NOS, not otherwise specified.

The percentage of *BRCA1/2* germline pathogenic variants detected by germline testing in period I did not differ significantly from those detected by the tumor-first approach in period II (8.0% vs 6.3%). This suggests that the effectiveness of both testing approaches is comparable regarding the proportion of germline pathogenic variants detected. However, changing testing strategies to the tumor-first approach greatly benefits both the medical centers and the patients. In this study, the proportion of patients receiving a germline test decreased from 69.0% in period I to 29.2% in period II. Considering the emotional stress, travel expenses, waiting time, and uncertainty that is related to germline testing, the tumor-first approach significantly alleviates the burden for a large proportion of patients and their relatives. These factors support the implementation of the tumor-first approach.

Suboptimal *BRCA1/2* testing rates have been reported in previous studies, ranging from 10% for genetic testing[13 14] to 80% for tumor testing.[8] The relatively high tumor testing rates of almost 80% were reported by Vos et al,[8] who performed an implementation study of the tumor-first approach. The pathologists involved were explicitly instructed to perform tumor-first testing for all patients, and the study reported an overall tumor testing rate of 77.6%. The real-world testing rates we reported after the implementation of the tumor-first approach were even higher: 81.0% of all patients was tested. With the University Medical Center Groningen being a recognized expert center for hereditary gynecological cancers, it is likely that our percentage of tested patients is relatively high compared with other medical centers. Nonetheless, our study suggests that up to almost 20% of the patients are not currently tested, and consequently a proportion of these women and their relatives may be missing out on optimal treatment and preventive strategies. Moreover, the gene panels used for tumor tests have been expanded during the past years by also including the moderate ovarian cancer risk genes *RAD51C*, *RAD51D*, *BRIP1*, and *PALB2*, and testing rates of these genes are also likely to be suboptimal.

To our knowledge, no research has been published investigating differences between tested and untested patients in the context of tumor-first testing. While the age of patients seemed to influence the likelihood of getting tested in period I by means of germline testing, the age of tested and untested patients did not differ in period II when tumor-first testing was performed. Nevertheless, testing rates were significantly lower in patients diagnosed with non-high-grade serous ovarian carcinoma in both periods of diagnosis, also in the currently active tumor-first approach. Since *BRCA1/2* pathogenic variants are most frequently detected in high-grade serous carcinoma, we expect a relatively smaller proportion of positive tests in the untested patients compared with the proportion reported in tested patients.

Disparities in general cancer predisposition testing have been reported previously. Van der Giessen et al[2] reported significant differences in educational level and migrant status between 700 newly referred counselees and the overall Dutch population. Our study did not report significant differences in educational level between tested and untested patients. However, the proportion of patients with a medium/higher education was notably greater among tested patients than among untested patients in period I with germline testing (44.5% vs 33.3%). The proportion of patients with a medium/higher education was more similar between tested and untested patients in period II with the tumor-first approach (54.7% vs 53.4%). This could indicate that educational level, like age, seems to affect the likelihood of receiving a germline test, but not the likelihood of receiving a tumor test.

Strengths and Weaknesses

Strengths of this study include the selection of a consecutive series of patients and the comparison of characteristics of tested versus untested patients in a real-world clinical setting. Differences in histotype and age were observed between tested and untested patients in the analysis combining period I and II. Differences in

Table 5 Patient and disease characteristics at baseline for tested and untested patients by period of diagnosis (period I and period II)

	Period I*			Period II*		
	Tested n=137	Untested n=33		Tested n=64	Untested n=15	
Characteristics	***N* (%)**	***N* (%)**	**P value**	***N* (%)**	***N* (%)**	**P value**
Age at diagnosis, median (IQR)	66.0 (58.0–72.0)	70.0 (66.0–75.0)	0.009	66.0 (59.0–72.0)	65.0 (56.0–78.0)	0.924
Year of diagnosis			0.417			0.555
2016	36 (26.3)	12 (36.4)		–	–	
2017	64 (46.7)	15 (45.5)		–	–	
2018	37 (27.0)	6 (18.2)		24 (37.5)	4 (26.7)	
2019	–	–		40 (62.5)	11 (73.3)	
BMI at diagnosis, kg/m^2			0.101			0.480
<18.5	1 (0.7)	2 (6.1)		4 (6.3)	1 (6.7)	
≥18.5 and ≤24.9	60 (43.8)	16 (48.5)		26 (40.6)	5 (33.3)	
≥25.0 and ≤29.9	41 (29.9)	12 (36.4)		24 (37.5)	4 (26.7)	
≥30	29 (21.2)	3 (9.1)		9 (14.1)	5 (33.3)	
Unknown	6 (4.4)	–		1 (1.6)	–	
Country of birth (self-reported)			0.841			1.000
The Netherlands	107 (78.1)	26 (78.8)		47 (73.4)	12 (80.0)	
Other	4 (2.9)	–		2 (3.1)	–	
Unknown	26 (19.0)	7 (21.2)		15 (23.4)	3 (20.0)	
Educational level† (self-reported)			0.612			0.329
Low	42 (30.7)	13 (39.4)		11 (17.2)	3 (20.0)	
Medium	57 (41.6)	10 (30.3)		35 (54.7)	7 (46.7)	
High	4 (2.9)	1 (3.0)		–	1 (6.7)	
Unknown	34 (24.8)	9 (27.3)		18 (28.1)	4 (26.7)	
Parity at diagnosis (self-reported)			0.811			0.051
Yes	91 (66.4)	20 (60.6)		40 (62.5)	6 (40.0)	
No	20 (14.6)	6 (18.2)		8 (12.5)	6 (40.0)	
Unknown	26 (19.0)	7 (21.2)		16 (25.0)	3 (20.0)	
Smoking status at diagnosis (self-reported)			0.679			0.677
Never smoker	54 (39.4)	15 (45.5)		25 (39.1)	6 (40.0)	
Former smoker	46 (33.6)	11 (33.3)		24 (37.5)	4 (26.7)	
Current smoker	14 (10.2)	1 (3.0)		4 (6.3)	2 (13.3)	
Unknown	23 (16.8)	6 (18.2)		11 (17.2)	3 (20.0)	
Family history of cancer at diagnosis (self-reported)			0.864			0.406
Yes	78 (56.9)	17 (51.5)		37 (57.8)	6 (40.0)	
No	36 (26.3)	10 (30.3)		16 (25.0)	5 (33.3)	
Unknown	23 (16.8)	6 (18.2)		11 (17.2)	4 (26.7)	
WHO performance status at diagnosis			0.199			1.000
0	77 (56.2)	20 (60.6)		36 (56.3)	9 (60.0)	
1	29 (21.2)	7 (21.2)		14 (21.9)	4 (26.7)	
2	5 (3.6)	2 (6.1)		6 (9.4)	1 (6.7)	

Continued

Table 5 Continued

Characteristics	Period I* Tested n=137 N (%)	Period I* Untested n=33 N (%)	P value	Period II* Tested n=64 N (%)	Period II* Untested n=15 N (%)	P value
3	1 (0.7)	2 (6.1)		–	–	
Unknown	25 (18.3)	2 (6.1)		8 (12.5)	1 (6.7)	
Frailty at diagnosis (GFI)			0.178			0.479
< 4 (non-frail)	62 (45.3)	14 (42.4)		29 (45.3)	9 (60.0)	
≥ 4 (frail)	23 (16.8)	10 (30.3)		13 (20.3)	1 (6.7)	
Unknown	52 (38.0)	9 (27.3)		22 (34.4)	5 (33.3)	
Histology at diagnosis			0.019			0.006
High-grade serous	103 (75.2)	17 (51.5)		47 (73.4)	5 (33.3)	
Non-high-grade serous	31 (22.6)	14 (42.4)		17 (26.6)	10 (66.7)	
Adenocarcinoma NOS	3 (2.2)	2 (6.1)		–	–	
FIGO stage at diagnosis			0.381			0.006
I/II	34 (24.8)	11 (33.3)		11 (17.2)	8 (53.3)	
III/IV	102 (74.5)	22 (66.7)		53 (82.8)	7 (46.7)	
Unknown	1 (0.7)	–		–	–	

One patient who rejected germline test was not included in analysis by testing status.
*Period I: January 1, 2016, until July 1, 2018. Period II: July 1, 2018, until January 1, 2020.
†Educational levels were defined as follows: low=primary or secondary education or less medium=vocational education; high=university or higher education.
BMI, body mass index; FIGO, International Federation of Gynecology Obstetrics; GFI, Groningen Frailty Index; IQR, Interquartile range; NOS, not otherwise specified.

histotype were also present when analyzing period I and II separately. These analyses were limited by the relatively small sample sizes of the groups in each period (n=171 and n=79), with only 15 untested patients in period II.

Implications for Practice and Future Research

Some clinicians may not offer *BRCA1/2* testing to all patients due to the assumption that *BRCA1/2* pathogenic variants are 'only' detected in high-grade serous carcinoma and that *BRCA1/2* germline carriers generally develop cancer at a younger age.[15 16] While all pathogenic variants in this study were detected in high-grade serous ovarian carcinoma, a recent meta-analysis by Witjes et al[15] indicated that *BRCA1/2* somatic and germline pathogenic variants can also be found in other histotypes. In addition, restricting *BRCA1/2* testing to histotypes in which pathogenic variants are most prevalent is highly dependent on the accuracy of histological classification and could lead to undesirable exclusion of misclassified patients. Furthermore, age of disease onset is reported to only slightly differ between *BRCA1/2* germline carriers and non-carriers. Besides age and histotype, a family history of breast or ovarian cancer is also not a suitable criterion for selecting patients for testing as approximately 30% of patients with a *BRCA1/2* germline pathogenic variant do not have a family history of breast or ovarian cancer.[17 18] For these reasons, all patients with epithelial ovarian cancer should be offered a tumor test, regardless of histotype, age, and family history. Nonetheless, the current study shows that adherence to these guidelines is not yet optimal and future research should focus on increasing test uptake.

CONCLUSION

Our analyses show suboptimal *BRCA1/2* testing rates in patients with epithelial ovarian cancer, even after implementation of the tumor-first approach. This can be attributed to suboptimal adherence of clinicians to guidelines recommending *BRCA1/2* testing in all patients with epithelial ovarian cancer as clinicians may deliberately choose not to test patients with non-high-grade serous carcinoma. Our findings can be used to optimize the care of patients with epithelial ovarian cancer and counseling of potentially affected family members. Awareness should be raised among clinicians on current guidelines and ways to increase uptake should be further investigated.

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