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Prediagnostic symptoms of ovarian carcinoma: A case-control study[1]

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Abstract

Objective—Women with ovarian carcinoma experience poor survival because symptoms are vague and diagnosis is unlikely at an early stage. The objective of this study was to identify a set of symptoms that might assist gynecologists and other clinicians in the diagnosis of localized ovarian carcinoma when treatment is most effective.

Methods—This population-based case-control study included 432 women, aged 19–88 years, with invasive ovarian carcinoma and 491 controls frequency-matched to cases on age, ethnicity, and interview time. Symptoms data were collected using interviewer-administered questionnaires. Odds ratios and 95% confidence intervals for the association of symptoms with ovarian carcinoma by stage and histology were estimated using unconditional multiple polytomous logistic regression models. The predictive ability of symptoms was evaluated by comparing the area under receiver operating curves (ROC).

Results—The following self-reported symptoms were significantly predictive of localized ovarian carcinoma irrespective of histological type: abdominal pain (ROC=0.81), distended and hard abdomen (ROC=0.83), vaginal bleeding not associated with periods (ROC=0.88), and a palpable abdominal mass (ROC=0.88). Urinary symptoms had low predictive ability, and bowel symptoms and fatigue/loss of appetite were predictive only at advanced stages. The best predictive ability was observed for a 4-symptom index that included abdominal pain, distended and hard abdomen, abdominal mass, and abnormal vaginal bleeding (ROC=0.90 sensitivity=74%; specificity=71%).

Conclusion—Greater awareness of the symptoms potentially related to ovarian cancer might lead to earlier diagnosis and might improve survival.

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

Keywords

Gynecologic oncology; Ovarian carcinoma diagnosis; Ovarian carcinoma symptoms; Case-control study

Introduction

Ovarian carcinoma is the eighth most common cancer and the fifth leading cause of cancer death among women in the United States [1]. Ovarian carcinoma causes more deaths than any other cancer of the female reproductive system, and the mortality rates for this cancer have not changed significantly since 1982 [2]. The 5-year relative survival rates currently are 92.7% for localized, 71.1% for regional, and 30.6% for distant disease [2]. Only 25% of women with ovarian carcinoma are diagnosed at a localized stage mostly due to the lack of specific symptoms and absence of accepted screening methods for early detection [3].

The premise that early-stage ovarian cancer is a silent disease has been revisited in recent years by advocacy groups and researchers [4]. Studies that reviewed medical records or health provider claims reported that the majority of women with ovarian cancer were symptomatic prior to their diagnosis (5–18). However, medical records and provider claims might underestimate the frequency, type, and duration of presenting symptoms [4;7]. Some investigators collected symptom data directly from patients with ovarian cancer [19–23], but did not use a control group. Case-control studies published to date [24–29] had a small number of invasive ovarian cancer cases, did not distinguish localized stage disease or histological type, and only one study was population-based [25].

The objective of this multiethnic, population-based, case-control study was to develop a symptom index that might assist gynecologists, oncologists, and other health care providers to diagnose ovarian cancer at an early stage when the prognosis is favorable. In particular, we focused on histologic-specific symptom presentation because serous carcinoma, the most common histological type of ovarian carcinoma, is considered to be asymptomatic in its early stages [30;31].

Methods

This study was conducted in Hawaii and included 432 women, aged 19–88 years, who were diagnosed with histologically-confirmed primary invasive ovarian carcinoma between 1993 and 2007 and 491 women without cancer. Eligible cases were identified through the rapid-reporting system of the Hawaii Tumor Registry, which is part of the Surveillance, Epidemiology, and End-Results Program of the National Cancer Institute. Information on tumor stage and histology was obtained from pathology and surgical reports. Eligible controls included women ages 18 years or older who were residents in Hawaii for a minimum of a year, had no prior history of ovarian cancer, and had at least one intact ovary. Control women were randomly selected from participants in an annual survey of representative households in Hawaii that is conducted by the Hawaii Department of Health under statutory provision and has participation rates close to 100%. Controls were frequency-matched to cases by age (5-year age groups), ethnicity, and interview time in an approximate 1:1 ratio. All women self-reported the race/ethnicity of their grandparents, and we assigned summary categories for race/ethnicity according to the following rules. A woman was classified into a particular ethnic group (e.g., Japanese) if all four of her grandparents were of this ethnic group. In agreement with a common rule applied in the State of Hawaii, [32] women with any Hawaiian background were classified as Native Hawaiian. Small numbers of Chinese, Korean, and other Asian women were

classified into the 'Other' ethnic group and were combined with women of mixed Caucasian/Asian ethnicity. The participation rate was 78% for cases and 80% for controls.

Interviews were conducted in the participant's home by a staff member who was uniformly trained and supervised to standardize interviewing and coding techniques. A structured pretested questionnaire was used to collect socio-demographic and health-related information, menstrual, reproductive, and gynecologic histories, and a history of exogenous hormone use. All women were asked whether they had had experienced any of the following 10 symptoms within 12 months prior to their diagnosis (for cases) or the time of interview (for controls): 1) persistent abdominal or pelvic pain or discomfort (further referred to as 'abdominal pain'); 2) unusual bowel irregularity such as diarrhea or constipation, flatulence, or bloating ('bowel symptoms'); 3) urinary frequency, difficulty emptying urinary bladder, or dysuria ('urinary symptoms'); 4) persistent distended and hard abdomen ('distended abdomen'); 5) persistent fatigue or loss of appetite ('fatigue/loss of appetite'); 6) persistent flank or back pain with or without exertion ('flank/back pain'); 7) vaginal bleeding not associated with periods ('abnormal vaginal bleeding'); 8) a palpable abdominal mass that woman herself had noticed ('abdominal mass'); 9) weight gain and swelling of the lower extremities (weight gain/leg swelling); and 10) nausea, vomiting, or heartburn ('nausea/heartburn'). The duration (in months) for each symptom experienced from onset to the date of diagnosis/interview was recorded. Quality control and performance of the interviewers was monitored by the project coordinator through a repeat interview of a random sample of 15% of participants. Women with cancer were interviewed within a median 8.9 months after diagnosis. During a period from interview to diagnosis, no second primary ovarian cancer or recurrence of the first primary ovarian cancer have occurred. All controls were free of cancer at the last follow-up in December of 2008.

The study was approved by the Institutional Review Board of the University of Hawaii. All study participants signed detailed consent forms.

Statistical analysis

The SAS software version 9.1.3 (SAS Institute Inc., Cary, NC) was used for data analysis. Unconditional multiple logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association of symptoms with ovarian carcinoma overall, and polytomous logistic regression models were used to compare presence/absence of symptoms among controls and cases by stage for each histological type. To compare the predictive potential of the symptoms, we computed the area under the receiver operating curve (ROC) which assesses the goodness-of-fit of logistic models [33]. The ROC is a plot of sensitivity (true positive rate) versus 'one minus specificity' (true negative rate). If prediction is perfect, both sensitivity and specificity are equal to one and the area under the curve equals one. If the test performs no better than chance, the area is equal to 0.5. Analysis of variance was used to compare number of symptoms and their duration. Variables were selected for inclusion into our final models based on the likelihood ratio statistic comparing model fit. Various symptoms were reported more often among women with higher education (weight gain and swelling of lower extremities: p=0.02), younger age (abdominal pain: p=0.01), Caucasian ethnicity (fatigue: p=0.002, back pain: 0.004; nausea/heartburn: p=0.03), who used contraceptive hormones (bowel irregularity, bloating: p=0.0005, and nausea: 0.01), who were nulliparous (abnormal vaginal bleeding: p=0.003), who were postmenopausal (abdominal pain: p=0.2). Time from diagnosis to interview was associated only with reporting fatigue; cases had a tendency to report fatigue more often with an increase in the time from the diagnosis to interview (p=0.02). Indicator variables for these subject characteristics were included in the final models. A history of tubal ligation and hysterectomy, and family history of breast or

ovarian cancer were associated with ovarian cancer risk, but did not affect symptom reporting. All pvalues were derived from two-tailed statistical tests at a significance level < 0.05.

Results

Demographic characteristics of 432 women with invasive ovarian carcinoma and 491 control participants are presented in Table 1. As expected from the study design, no statistically significant differences in age or ethnicity between two groups were observed. The average age among women with cancer and controls was 55.6 ± 0.6 years and 56.7 ± 0.6 years, respectively. Women with ovarian carcinoma were less educated, had fewer children, were less likely to use contraceptive hormones, and were more likely to be postmenopausal than controls. Among postmenopausal women, women with ovarian carcinoma were more likely to use hormone replacement therapy than were controls. Only one-third of women with cancer were diagnosed at a localized stage, and serous carcinoma was the most prevalent tumor histological type.

Predictive ability of individual symptoms

Women diagnosed with ovarian carcinoma, including cases with a localized stage, were significantly more likely than controls to report abdominal pain; distended and hard abdomen; abdominal mass; abnormal vaginal bleeding; and urinary symptoms (Table 2). Among these symptoms, abdominal mass, abnormal vaginal bleeding, and distended and hard abdomen had the best predictive ability (ROC for localized stage of ovarian carcinoma: 0.88, 0.88, and 0.83, respectively). These symptoms were rarely reported by women without cancer, but were relatively common among cases (among cases with a localized disease, 36% reported having a distended and hard abdomen, 16% noticed an abdominal mass, and 13% experienced abnormal vaginal bleeding). Abdominal pain (ROC: 0.81) was the most common symptom among cases with a localized carcinoma (sensitivity: 49%); however, it was also reported by 18% of controls (specificity: 82%). The predictive ability of urinary symptoms was somewhat lower (ROC for localized stage was 0.76; sensitivity: 31%; specificity: 78%). Significant differences between cases and controls in reported fatigue/loss of appetite and bowel symptoms were limited to cases at an advanced stage of disease. No differences between cases and controls were found in reported flank or back pain; weight gain and swelling of the extremities; or nausea, vomiting, heartburn, and indigestion.

Number and combination of symptoms

Women with ovarian cancer were significantly more likely than were controls to report a higher number symptoms (mean, 3.6±0.1 vs. 2.6±0.1; p <0.0001). Cases were more likely to present with a combination of abdominal pain with the following symptoms: bowel symptoms, fatigue/loss of appetite, urinary symptoms, or distended and hard abdomen (Table 2). Although combinations of symptoms had a higher specificity when compared to the specificity of individual symptoms, their sensitivity was lower and the predictive ability was not improved.

Comparison of a predictive ability of symptom indices

We examined the predictive ability of various symptom indices shown in Table 2. The best predictive ability was observed for a 4-symptom index that included abdominal pain, distended and hard abdomen, abdominal mass, and abnormal vaginal bleeding (ROC=0.90); and a 3-symptom index including distended and hard abdomen, abdominal mass, and abnormal vaginal bleeding (ROC=0.90). The 4-symptom index had a 74% sensitivity and a 77% specificity. Including the duration of symptoms into any index resulted in reduced sensitivity with little to no improvement in predictive value (data not shown). Although, the specificity of the 3-symptom index was 93%, its sensitivity was low (54%).

Symptom duration

With the exception of abnormal bleeding, all symptoms were of a significantly shorter duration among ovarian cancer cases compared to controls (Table 3). The risk of having any of the symptoms for 12 months or longer was significantly lower among women with ovarian carcinoma than among controls.

Individual symptoms and symptom indices by histological type

The largest variation in reported symptoms by histological type of cancer was for distended and hard abdomen and for abdominal mass. These symptoms were more common among women with mucinous carcinoma than among women with other histological types of ovarian cancer, but the differences were not statistically significant (Table 4). Abnormal vaginal bleeding was more likely to be reported by women with endometrioid carcinoma, followed by women with clear cell, serous, and mucinous tumors. Most of these symptoms were as likely to be present among women with early-stage as late-stage tumors.

For all histological types, the ROC ranged from 0.92 to 0.97 for localized stage and from 0.89 to 0.96 for all stages combined. With the exception of endometrioid carcinoma, the 3- and 4-symptom indices had similar predictive ability for all histological types. Both indices included only significantly predictive symptoms for localized stage for all histological types with the exception of abnormal vaginal bleeding, which was not a significant predictor of localized clear cell carcinoma.

Discussion

A unique aspect of our analysis was the ability to compare symptoms among controls and cases presenting at a localized stage of ovarian cancer (stages IA and IB), as well as to perform a subgroup analysis by stage for the main ovarian cancer histological types. Importantly, we observed significant differences in symptoms reported by controls and women diagnosed at localized stages independently of tumor histological type. This finding may be relevant to the clinician's ability to diagnose this lethal malignancy at a time when therapeutic intervention is most effective.

Our investigation confirmed findings from other case-control studies that women with ovarian cancer are significantly more likely than population controls to experience at least one of several symptoms previously identified as being relevant to the diagnosis of this malignancy [24–28].

Women with ovarian cancer were more likely than controls to complain of abdominal or pelvic pain or discomfort, distended and hard abdomen, urinary symptoms, abnormal vaginal bleeding, and palpable abdominal mass. In addition to these symptoms, women with advanced disease were more likely than controls to experience bowel irregularity, bloating, or flatulence; and fatigue or/and loss of appetite.

Similar to our study, abdominal pain was one of the most common symptom reported in previous investigations [4;12–14;16;18;20;26;29;34]. Distended abdomen (or increased abdominal girth, abdominal swelling) has also been found to be a common symptom in a number of studies [7;8;13;18;19;34]. Abnormal vaginal bleeding was significantly more often reported by cases in our investigation (consistent with the observation by Vine et al. [25]), but it was not a common symptom. In accord with our study, bowel symptoms were found to be a late-stage symptom by several investigators [8;17;20–23]. As in other studies, we found that cases were more likely than controls to have multiple symptoms [19;25] and to have a shorter duration of symptoms [20;24;25]. With the exception of abnormal vaginal bleeding, a shorter duration of symptoms among cases might reflect a more abrupt onset.

The composition of the comparison population is critical to determining the relevance of a particular symptom to the diagnosis of ovarian cancer. In the North Carolina study [25] which was the largest published investigation on this subject before the present study, controls complained less than our comparison group regarding abdominal pain or discomfort and urinary symptoms, but similarly with regard to abdominal distention and abnormal vaginal bleeding. Controls, who were selected among clinic visitors by Goff et al. [26] more often reported abdominal pain (30%) and urinary symptoms (32%) than did controls in Hawaii, but did not differ from our controls or North Carolina study controls in reporting abnormal vaginal bleeding (4%).

Persistent distended and hard abdomen might reflect the presence of ascites. Shen-Gunther et al. [35] investigated ascites as a predictor of ovarian malignancy among 125 patients with ovarian carcinoma, including 56 women with invasive tumors, from two hospitals and concluded that the presence of preoperative ascites was highly predictive of ovarian malignancy. The positive and negative predictive values reported by this group for ascites were 95% and 73%, respectively. A progressive relationship between stage of ovarian cancer and proportion of cases with ascites was identified. Similar to our findings, Shen-Gunther et al. [35] reported that a lower percentage of women with endometrioid carcinoma presented with true ascites (25% vs. 29% in our study). There is some evidence from clinical studies in support of our finding that endometrioid carcinomas more often present with vaginal bleeding [30; 31].

The possibility of recall bias cannot be excluded in interpreting the results of this investigation as women with ovarian cancer might over-report symptoms. All eligible cases were identified through rapid case ascertainment by personnel at the Hawaii Tumor Registry, but we did not have the opportunity to interview them prior to diagnosis. Knowledge of their diagnosis might have influenced how women ‘remembered’ symptoms. However, when we explored the relation of time from diagnosis to interview with symptom reporting, only fatigue appeared to be differentially affected; fatigue was positively associated with the interval of time from diagnosis to interview. Because a prospective design is not suitable for studies of symptoms preceding rare diseases, several studies attempted to reduce recall bias by obtaining symptom data using review of medical records [12;13] or Medicare provider claims of cases and controls [34], or interviewing cases diagnosed with an ovarian mass before definitive cancer diagnosis [26]. Although the frequency and types of symptom and diagnostic codes in medical records and claims data are likely to underestimate symptom reporting obtained from direct communication with the patient, [4;34] resulting in lower estimates of association of ‘target’ ovarian symptoms with risk, all studies revealed an excess of similar symptoms for cases.

Ovarian cancer is a disease that is difficult to detect in its early stages due to nonspecific symptoms. In this study, we present evidence that the majority of women with localized ovarian cancer, independently of tumor histological type, experienced at least one symptom potentially related to ovarian cancer several months prior to their diagnosis. More than a half of the women with ovarian cancer in our study presented with symptoms that were uncommon among controls, such as distended and hard abdomen, abnormal vaginal bleeding, and noticeable abdominal mass. Obviously, these symptoms might be related to other diseases and their predictive value is reduced by the rarity of ovarian cancer. Nonetheless, women should be encouraged by gynecologists and other health care providers to seek medical attention soon after onset of these symptoms, especially if they are at high risk of ovarian cancer through genetic predisposition or other risk factors (e.g., nulligravidity, not using contraceptive hormones, infertility, history of endometriosis). Ovarian cancer might be considered in a differential diagnosis if symptoms are unexplained by other underlying diseases. Earlier diagnosis of an invasive ovarian carcinoma might also be possible if women experiencing a combination of symptoms, such as abdominal pain with urinary symptoms; persisting fatigue;

or bowel irregularity and bloating are encouraged to seek gynecologic evaluation. Differences in symptom presentation by histological type need further evaluation in a larger study.

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Table 1

Participant characteristics

Characteristics	Cases (n=432) No. (%)	Controls (n=491) No. (%)	P value for the chi-square test
Age, years			
< 45	75 (17)	93 (19)	
45–54	121 (28)	140 (29)	
55–64	113 (26)	144 (29)	
≥ 65	123 (29)	114 (23)	0.30
Ethnicity			
Caucasian	104 (24)	114 (23)	
Japanese	122 (28)	137 (28)	
Hawaiian	59 (14)	107 (14)	
Filipina	84 (19)	68 (22)	
Other	63 (15)	65 (13)	0.91
Education, years			
≤ 12	172 (40)	155 (32)	
13–14	133 (31)	162 (33)	
≥ 15	127 (29)	174 (35)	0.03
Parity			
nulliparous	119 (28)	76 (15)	
1–2	167 (39)	190 (39)	
3 or more	146 (34)	225 (46)	<0.0001
Used contraceptive hormones	185 (43)	330 (67)	<0.0001
Postmenopausal	306 (71)	312 (64)	0.02
Used menopausal hormones	178 (58)	149 (48)	0.01
Stage at diagnosis			
localized (IA and IB)	128 (30)		
regional (IC and II)	111 (26)		
distant (III–IV)	182 (42)		
not available	11 (2)		
Tumor histological type			
serous	196 (45)		
endometrioid	75 (17)		
clear cell	52 (12)		
mucinous	45 (10)		
mixed	11 (3)		
other	53 (12)		

Table 2

Symptoms reported by study participants during 12 months prior to diagnosis (cases) or interview date (controls)

				Cases by stage at diagnosis (n=421)						ROC	
	Controls (n=491)	Cases (n=432)		localized (n=128)		regional (n=111)		advanced (n=182)			
Reported symptoms	n (%)	n (%)	OR (CI) [a]	n (%)	OR (CI)[a]	n (%)	OR (CI) [a]	n (%)	OR (CI) [a]	All	Localized stage only
Significant predictors of localized stage											
Abdominal pain	89 (18)	238 (55)	6.5 (4.7–9.1)	63 (49)	4.9 (3.1–7.6)	56 (50)	5.6 (3.6–9.0)	113 (62)	8.4 (5.6–12.7)	0.79	0.81
Distended abdomen	17 (3)	176 (41)	21.1 (11.4–32.3)	46 (36)	15.9 (8.4–30.0)	41 (37)	18.2 (9.5–34.7)	85 (47)	28.2 (15.6–51.0)	0.81	0.83
Abdominal mass	6 (1)	70 (16)	24.1 (10.0–58.1)	20 (16)	26.3 (9.7–71.1)	21 (19)	23.6 (8.0–61.9)	27 (15)	24.4 (9.4–62.9)	0.84	0.88
Abnormal bleeding	17 (3)	55 (13)	6.4 (3.5–11.8)	17 (13)	7.3 (3.4–15.8)	17 (15)	6.1 (2.9–12.8)	19 (10)	5.8 (2.8–12.2)	0.83	0.88
Urinary symptoms	107 (22)	143 (33)	1.9 (1.4–2.6)	40 (31)	1.9 (1.2–2.9)	35 (32)	1.8 (1.1–2.9)	62 (34)	1.9 (1.3–2.8)	0.70	0.76
Significant predictors of regional/advanced stages											
Bowel symptoms	212 (43)	184 (43)	1.1 (0.8–1.4)	42 (33)	0.7 (0.4–1.1)	42 (38)	0.8 (0.5–1.3)	96 (53)	1.6 (1.1–2.4)	n/s	n/s
Fatigue/appetite loss	115 (23)	166 (38)	2.2 (1.6–2.9)	40 (31)	1.5 (0.9–2.4)	41 (37)	2.1 (1.3–3.3)	82 (45)	2.8 (1.9–4.1)	0.72	n/s
Not significant predictors											
Flank or back pain	183 (37)	87 (20)	0.6 (0.4–0.8)	20 (16)	0.5 (0.3–0.8)	28 (25)	0.7 (0.4–1.1)	37 (10)	0.6 (0.3–0.9)	n/s	n/s
Weight gain/leg swelling	118 (24)	62 (14)	0.9 (0.7–1.4)	18 (14)	1.1 (0.6–2.1)	23 (21)	1.1 (0.7–1.9)	18 (10)	0.8 (0.4–1.3)	n/s	n/s
Nausea/heartburn	114 (23)	69 (16)	1.1 (0.7–1.6)	18 (14)	1.1 (0.6–1.9)	22 (20)	1.1 (0.6–1.8)	27 (15)	1.2 (0.7–2.1)	n/s	n/s
Symptom Indices											
7-symptom index [b]	293 (60)	368 (85)	7.4 (4.6–11.8)	102 (80)	5.7 (4.0–15.1)	98 (88)	7.8 (4.0–15.1)	160 (88)	11.6 (6.0–33.7)	0.86	0.89
5-symptom index [c]	182 (37)	344 (80)	9.9 (6.6–14.8)	96 (75)	7.9 (4.6–13.8)	92 (83)	11.0 (6.3–19.9)	148 (81)	11.8 (6.9–20.2)	0.89	0.91
4-symptom index [d]	114 (23)	320 (74)	12.4 (8.4–18.3)	88 (69)	9.1 (5.4–15.5)	84 (76)	13.1 (7.8–27.3)	141 (77)	15.5 (9.3–15.8)	0.90	0.91
3-symptom index [e]	35 (7)	234 (54)	19.5 (12.4–30.7)	65 (51)	16.9 (9.7–29.7)	59 (54)	17.1 (9.9–29.5)	105 (58)	26.0 (15.3–44.3)	0.90	0.91
Abdominal pain in combination with:											
Urinary symptoms	29 (6)	96 (22)	5.1 (3.2–8.1)	23 (18)	3.9 (2.1–7.2)	19 (17)	3.8 (2.0–7.3)	50 (27)	6.6 (3.8–7.3)	0.74	0.77
Bowel symptoms	62 (13)	131 (30)	3.1 (2.2–4.2)	29 (23)	2.1 (1.3–3.6)	24 (22)	2.1 (1.3–3.7)	76 (42)	5.4 (3.5–6.2)	0.73	0.76
Fatigue/appetite loss	42 (9)	115 (27)	4.1 (2.7–6.1)	26 (20)	2.8 (1.6–4.9)	21 (19)	2.8 (1.5–5.1)	65 (36)	6.1 (3.8–9.7)	0.73	0.76
Distended abdomen	5 (1)	120 (28)	40.9 (16.3–102)	32 (25)	31.9 (11.8–85.9)	22 (20)	27.2 (10.0–75.3)	63 (35)	59.7 (23.0–154)	0.78	0.82

Abbreviations: ROC, area under the receiver operating curve; OR, odds ratio; 95% CI, confidence interval; n/s, not a significant predictor

[a] Adjusted for age, ethnicity, education, parity, menopausal status, and use of contraceptive and menopausal hormones.

[b] Includes any one of the following symptoms: 1/distended abdomen, 2/abnormal vaginal bleeding, 3/palpable abdominal mass, 4/abdominal pain, 5/urinary symptoms, 6/bowel symptoms, and 7/fatigue/appetite loss.

[c] Includes any one of the following symptoms: 1/distended abdomen, 2/abnormal vaginal bleeding, 3/palpable abdominal mass, 4/abdominal pain, and 5/urinary symptoms.

[d] Includes any one of the following symptoms: 1/distended abdomen, 2/abnormal vaginal bleeding, 3/palpable abdominal mass, and 4/abdominal pain.

[e] Includes any one of the following symptoms: 1/distended abdomen, 2/abnormal vaginal bleeding, and 3/palpable abdominal mass.

Table 3

Duration of symptoms reported by study participants prior to diagnosis (cases) or reference date (controls)

					Cases by stage at diagnosis (n=421)					
					localized (n=128)		regional (n=111)		distant (n=182)	
Symptom duration (months)	**Controls (n=491)**	**Cases (n=432)**	**OR (95% CI) [a]**	**P [b]**		**OR (95% CI) [a]**		**OR (95% CI) [a]**		**OR (95% CI) [a]**
Abdominal pain, mean ±SE	4.9±0.4	3.7± 0.4		0.01	3.5± 0.4		4.1± 0.5		3.6± 0.3	
n (%) with duration ≥ 12 months	18 (20)	24 (10)	0.4 (0.2 – 0.9)		4 (6)	0.3 (0.1 – 0.9)	7 (13)	0.6 (0.2 – 1.6)	13 (12)	0.5 (0.2 – 1.2)
Bowel symptoms, mean (SE)	5.7± 0.3	3.5± 0.3		<0.0001	3.4 (0.7)		3.3 (0.6)		3.5 (0.4)	
n (%) with duration ≥ 12 months	68 (32)	21 (11)	0.2 (0.1 – 0.4)		7 (17)	0.4 (0.2 – 0.9)	5 (12)	0.3 (0.1 – 0.7)	8 (8)	0.2 (0.1 – 0.4)
Distended abdomen, mean (SE)	6.7± 0.7	3.2± 0.2		<0.0001	3.6 (0.5)		3.6 (0.5)		2.6 (0.3)	
n (%) with duration ≥ 12 months	7 (41)	13 (7)	0.1 (0.1 – 0.4)		4 (9)	0.2 (0. 1– 0.8)	4 (10)	0.1 (0.1 – 0.7)	4 (5)	0.1 (0.1 – 0.3)
Urinary symptoms, mean (SE)	7.6± 0.4	4.4± 0.4		<0.0001	4.3 (0.7)		4.9 (0.7)		4.2 (0.5)	
n (%) with duration ≥ 12 months	53 (49)	26 (18)	0.3 (0.2 – 0.5)		6 (15)	0.2 (0.1 – 0.6)	7 (20)	0.3 (0.1 – 0.7)	11 (18)	0.3 (0.1 – 0.6)
Fatigue/appetite loss, mean (SE)	6.7± 0.4	4.1± 0.3		<0.0001	4.2 (0.6)		4.2 (0.6)		3.8 (0.4)	
n (%) with duration ≥ 12 months	42 (37)	23 (14)	0.3 (0.1 – 0.5)		4 (10)	0.2 (0.1 – 0.6)	7 (17)	0.3 (0.1 – 0.9)	10 (12)	0.2 (0.1 – 0.4)
Abnormal bleeding, mean (SE)	2.4± 0.8	4.3± 0.5		0.05	5.3 (0.9)		4.6 (0.8)		3.5 (0.9)	
n (%) with duration ≥ 12 months	0 (0)	9 (16)	n/a		4 (24)	n/a	2 (12)	n/a	3 (16)	n/a
Abdominal mass, mean (SE)	10.9± 1.5	3.0± 0.5		<0.0001	2.9 (1.1)		2.5 (0.8)		3.2 (0.8)	
n (%) with duration ≥ 12 months	5 (83)	8 (11)	0.1 (0.1 – 0.3)		3 (15)	0.1 (0.1 – 0.6)	3 (14)	0.1 (0.1 – 0.3)	1 (4)	n/a

Abbreviations: n/a, risk estimates are not available due to an absence of controls in a subgroup.

[a] OR and 95% CI for a risk of having a given symptom for 12 months or longer vs. less than 12 months (adjusted for age, ethnicity, education, parity, menopausal status, and use of contraceptive and menopausal hormones).

[b] P from analysis of variance (ANOVA) comparing means of symptom duration among cases and controls

Table 4

Symptoms reported by study participants during 12 months prior to diagnosis (cases) or interview date (controls) by tumor histological type

Symptoms	Controls n (%)	Cases n (%)		Cases by stage at diagnosis						ROC	
				localized		regional		distant			
			OR (95% CI)[a]	n (%)	OR (95% CI) [a]	n (%)	OR (95% CI) [a]	n (%)	OR (95% CI) [a]	All cases	Localized stage only
						Serous carcinoma					
No. of participants	491(71)	196 (29)		21 (11)		43 (22)		128 (67)			
Abdominal pain	89 (18)	115 (59)	7.6 (5.1–11.5)	13 (62)	8.6 (3.3–22.6)	21 (49)	5.9 (2.9–11.7)	78 (61)	8.1 (5.1–12.9)	0.80	0.86
Distended abdomen	17 (3)	80 (41)	21.0 (11.5–38.4)	6 (29)	10.4 (3.3–32.2)	15 (35)	17.8 (8.6–41.9)	57 (45)	24.2 (12.7–46.0)	0.81	0.86
Abdominal mass	6 (1)	35 (18)	26.7 (10.1–70.3)	5 (23)	50.6 (11.8–217)	8 (19)	24.0 (7.2–79.2)	21 (16)	77.1 (9.6–76.7)	0.86	0.94
Abnormal bleeding	17 (3)	17 (9)	4.8 (2.2–10.6)	2 (9)	6.0 (1.1–31.2)	4 (9)	3.7 (1.1–12.2)	11 (9)	5.7 (2.3–13.9)	0.83	0.94
Urinary symptoms	107 (22)	72 (37)	2.1 (1.5–3.0)	10 (48)	3.3 (1.4–7.9)	13 (30)	1.6 (0.8–3.1)	46 (36)	2.1 (1.3–3.1)	0.72	0.79
Bowel symptoms	212 (43)	100 (51)	1.5 (1.1–2.1)	12 (57)	1.8 (0.7–4.6)	19 (44)	1.1 (0.6–2.1)	68 (53)	1.6 (1.1–2.5)	0.70	n/s
Fatigue/loss of appetite	115 (23)	76 (39)	2.1 (1.4–3.0)	9 (43)	2.5 (0.9–6.5)	13 (30)	1.6 (0.8–3.4)	52 (41)	2.1 (1.4–3.3)	0.71	0.78
4-symptom index	114 (43)	148 (76)	13.5 (7.9–23.1)	15 (71)	10.2 93.3–31.3)	32 (74)	14.6 (6.6–32.4)	98 (77)	14.5 (7.6–27.6)	0.91	0.96
3-symptom index	35 (7)	107 (55)	21.4 (12.2–37.7)	10 (48)	16.3 (5.6–47.2)	23 (53)	20.6 (9.5–44.7)	72 (56)	25.1 (13.2–48.0)	0.91	0.95
						Endometrioid carcinoma					
No. of participants	491(85)	75 (15)		25 (35)		33 (46)		14 (19)			
Abdominal pain	89 (18)	41 (55)	8.8 (4.7–16.3)	14 (56)	9.3 (3.5–24.2)	18 (55)	8.6 (3.7–19.7)	8 (57)	10.2 (3.0–35.4)	0.84	0.87
Distended abdomen	17 (3)	22 (29)	9.0 (4.0–20.1)	8 (32)	9.5 (3.1–28.5)	11 (33)	13.7 (4.9–38.1)	3 (21)	5.4 (1.1–23.9)	0.80	0.86
Abdominal mass	6 (1)	7 (9)	17.2 (4.7–63.5)	2 (8)	17.1 (2.5–117.2)	5 (15)	17.6 (4.3–72.2)	0 (0)	n/a	0.86	0.92
Abnormal bleeding	17 (3)	15 (20)	8.6 (3.4–21.8)	4 (16)	8.8 (2.1–36.0)	7 (21)	7.5 (2.5–22.4)	3 (21)	10.2 (1.9–55.7)	0.88	0.94
Urinary symptoms	107 (22)	20 (27)	1.5 (0.8–2.7)	3 (12)	0.5 (0.2–1.9)	10 (30)	1.7 (0.8–3.9)	6 (43)	3.5 (1.1–10.9)	n/s	n/s
Bowel symptoms	212 (43)	24 (32)	0.6 (0.3–1.1)	8 (32)	0.6 (0.2–1.4)	8 (24)	0.4 (0.2–0.9)	7 (50)	1.5 (0.5–4.2)	n/s	n/s
Fatigue/loss of appetite	115 (23)	25 (33)	1.7 (0.9–3.1)	9 (36)	1.9 (0.8–4.7)	10 (30)	1.5 (0.6–3.3)	6 (43)	2.7 (0.9–8.3)	n/s	n/s
4-symptom index[c]	114 (23)	55 (73)	15.5 (6.9–34.7)	18 (72)	17.3 (4.8–62.3)	26 (79)	21.0 (7.5–58.8)	10 (71)	13.5 (2.9–63.4)	0.92	0.95
3-symptom index[d]	35 (7)	35 (47)	11.6 (5.5–24.6)	12 (48)	13.3 (4.4–40.7)	16 (48)	12.5 (5.2–30.0)	6 (43)	8.2 (2.1–32.1)	0.89	0.95
						Mucinous carcinoma					
No. of participants	491(92)	45 (8)		36 (80)		6 (13)		3 (7)			
Abdominal pain	89 (18)	23 (51)	5.3 (2.6–10.8)	19 (53)	5.0 (2.5–10.1)	3 (50)	4.5 (0.9–22.7)	1 (33)	n/a	0.84	0.83
Distended abdomen	17 (3)	25 (56)	34.8 (16.3–74.6)	20 (56)	34.9 (15.4–78.8)	4 (67)	55.8 (9.5–325)	1 (33)	n/a	0.91	0.90

Symptoms	Controls n (%)	Cases n (%)		Cases by stage at diagnosis						ROC	
				localized		regional		distant			
			OR (95% CI)[a]	n (%)	OR (95% CI) [a]	n (%)	OR (95% CI) [a]	n (%)	OR (95% CI) [a]	All cases	Localized stage only
Abdominal mass	6 (1)	8 (18)	49.5 (12.6–194.1)	5(14)	41.2 (9.7–175.5)	2 (33)	164 (11.0–175)	1 (33)	n/a	0.96	0.96
Abnormal bleeding	17 (3)	4 (9)	6.9 (1.8–27.3)	3 (8)	6.6 (1.4–30.9)	1 (7)	6.4 (0.5–84.9)	0 (0)	n/a	0.91	0.94
Urinary symptoms	107 (22)	12 (27)	1.3 (0.7–2.6)	11 (31)	1.6 (0.8–3.3)	1 (17)	0.7 (0.1–6.2)	0 (0)	n/a	n/s	n/s
Bowel symptoms	212 (43)	15 (33)	0.7 (0.3–1.3)	14 (39)	0.8 (0.4–1.7)	1 (17)	0.3 (0.1–1.3)	0 (0)	n/a	n/s	n/s
Fatigue/loss of appetite	115 (23)	9 (20)	0.8 (0.4–1.7)	8 (22)	0.9 (0.4–2.1)	1 (17)	0.7 (0.1–5.7)	0 (0)	n/a	n/s	n/s
4-symptom index[c]	114 (23)	33 (73)	18.1 (5.4–61.0)	26 (72)	18.1 (4.4–74.7)	5 (83)	17.3 (1.8–171)	2 (67)	n/a	0.95	0.97
3-symptom index[d]	35 (7)	26 (58)	33.0 (10.7–101.4)	21 (58)	41.2 (10.6–160)	4 (67)	23.4 (3.1–177)	1 (33)	n/a	0.96	0.97
				Clear cell carcinoma							
No. of participants	491(90)	52 (10)		31 (60)		9 (17)		12 (23)			
Abdominal pain	89 (18)	19 (37)	3.3 (1.6–6.5)	11 (35)	3.5 (1.5–8.3)	2 (22)	1.7 (0.3–9.4)	6 (50)	4.2 (1.3–14.1)	0.79	0.82
Distended abdomen	17 (3)	17 (33)	12.9 (5.2–31.7)	8 (26)	7.3 (2.4–21.9)	1 (11)	2.8 (0.3–31.9)	8 (67)	67.3 (15.2–297)	0.82	0.81
Abdominal mass	6 (1)	8 (15)	16.3 (4.5–59.7)	7 (23)	25.7 (6.4–103.0)	0 (0)	n/a	1 (8)	7.2 (0.7–73.8)	0.92	0.91
Abnormal bleeding	17 (3)	6 (12)	4.2 (1.2–15.1)	2 (6)	1.7 (0.2–12.1)	3 (33)	25.1 (3.2–195.8)	1 (8)	4.5 (0.3–58.1)	0.92	n/s
Urinary symptoms	107 (22)	16 (31)	1.9 (0.9–3.8)	9 (29)	1.8 (0.8–4.4)	3 (33)	2.1 (0.5–9.6)	4 (33)	2.1 (0.6–7.2)	n/s	n/s
Bowel symptoms	212 (43)	10 (19)	0.3 (0.1–0.7)	4 (13)	0.2 (0.1–0.6)	3 (33)	0.9 (0.2–3.8)	3 (25)	0.4 (0.1–1.5)	n/s	n/s
Fatigue/loss of appetite	115 (23)	18 (35)	1.9 (0.9–3.6)	7 (23)	0.9 (0.4–2.5)	5 (56)	6.0 (1.3–27.6)	6 (50)	3.6 (1.1–12.4)	n/s	n/s
4-symptom index[c]	114 (23)	32 (62)	5.9 (2.4–14.5)	19 (61)	5.5 (1.9–15.4)	5 (56)	9.2 (1.7–49.8)	8 (67)	6.0 (1.2–28.8)	0.93	0.92
3-symptom index[d]	35 (7)	26 (50)	12.1 (4.6–31.8)	14 (45)	8.8 (2.9–26.2)	4 (44)	23.6 (3.8–148.2)	8 (67)	37.6 (6.4–222.3)	0.94	0.92

Abbreviations: ROC, area under receiver operating curve; OR, odds ratio; CI, confidence interval

[a] OR and 95% CI for a difference in reporting a given symptom between control women (OR=1.0) and women with cancer adjusted for age, ethnicity, education, parity, menopausal status, and use of contraceptive and menopausal hormones.

[b] Includes any of the following symptoms: 1/distended abdomen, 2/abnormal vaginal bleeding, 3 abdominal mass, 4/abdominal pain, 5/urinary symptoms, 6/bowel irregularity or bloating, 7/fatigue or loss of appetite.

[c] Includes any one of the following symptoms: 1/distended abdomen, 2/abnormal vaginal bleeding, 3/abdominal mass, 4/abdominal pain.

[d] Includes any one of the following symptoms: 1/distended abdomen, 2/abnormal vaginal bleeding, 3/abdominal mass.