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ARTICLE

Predictive Value of Symptoms for Early Detection of Ovarian Cancer

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Background A recent consensus statement encouraged use of certain symptoms to diagnose ovarian cancer earlier. We assessed the sensitivity, specificity, and positive predictive value of a proposed symptom index and of symptoms included in the consensus recommendation.

Methods In-person interviews were conducted with 812 case patients, aged 35–74 years, who had epithelial ovarian cancer that was diagnosed from January 1, 2002, through December 31, 2005, and with 1313 population-based control subjects. The symptom index was considered positive when pelvic or abdominal pain or bloating or feeling full was reported at least daily for at least 1 week, with an onset of less than 12 months before diagnosis or a reference date (for control subjects). The consensus criteria were considered fulfilled when any symptom above or urinary urgency or frequency was reported for at least 1 month, with an onset of less than 12 months before diagnosis or a reference date. Positive predictive value was calculated by use of external estimates of cancer prevalence.

Results Most case patients who had a positive index or met consensus criteria did so only within 5 months before diagnosis. Symptoms (except nausea) were somewhat less likely to have occurred among women diagnosed with early-stage than late-stage ovarian cancer. The estimated positive predictive value of the symptom index or symptoms meeting the consensus criteria was 0.6%–1.1% overall and less than 0.5% for early-stage disease.

Conclusion Use of symptoms to trigger medical evaluation for ovarian cancer is likely to result in diagnosis of the disease in only one of 100 women in the general population with such symptoms.

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In 2007, prompted by recent reports (1–5), the Gynecologic Cancer Foundation, the Society of Gynecologic Oncologists, and the American Cancer Society released a consensus statement on ovarian cancer symptoms (available at http://www.wcn.org/articles/types_of_cancer/ovarian/symptoms/concensus_statement.html) (6). The statement notes that certain symptoms—including bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary urgency or frequency—are much more likely to be present in patients with ovarian cancer than in women in the general population and also that symptoms in women with ovarian cancer are persistent yet represent a change from an individual's normal baseline (6). The statement recommends that a woman who experiences the above-mentioned symptoms almost daily for more than a few weeks should consult her physician, with the hope that prompt evaluation may lead to earlier diagnosis of ovarian cancer and improved outcomes. The recommendation follows closely from the findings of Goff et al. (2), who developed a "symptom index." The symptom index was considered positive when one or more symptoms (of pelvic or abdominal pain, increased abdominal size or bloating, and difficulty eating or feeling full) had been present for less than 1 year but for more than 12 days per month.

Concerns have been raised, however, regarding the ability of symptom recognition to result in detection of ovarian cancer at an earlier stage or to confer a survival benefit and the anticipated increases in associated health-care costs (6). The imperfect specificity of symptoms for detecting ovarian cancer and the relatively low prevalence of this disease indicate that most women with symptoms will not have ovarian cancer. In a large population-based study, we examined the occurrence and timing of symptoms in women with epithelial ovarian cancer and in control subjects. We assessed the sensitivity, specificity, and positive predictive value of approximations of Goff's symptom index (2) and of symptoms included in the consensus recommendation.

Patients and Methods

The study population and methods have been described previously (7). Briefly, women who resided in a 13-county area of western Washington State, who were aged 35–74 years, and who were diagnosed with a primary invasive or borderline epithelial ovarian tumor from January 1, 2002, through December 31, 2005, were identified through a population-based registry that is part of the

Surveillance, Epidemiology, and End Results program of the US National Cancer Institute. Of 1058 eligible women identified, 812 (76.6%) were interviewed; one woman (with invasive disease) failed to complete the symptoms portion of the interview. The tumor histologies were coded from pathology reports by the registry staff according to the third edition of the *International Classification of Diseases for Oncology* (*ICD-O*) (8). Control subjects (with at least one ovary and no history of ovarian cancer) were selected by random digit dialing (9) that used stratified sampling in 5-year age categories, 1-year calendar intervals, and two (urban vs suburban or rural) county strata. We interviewed 1313 women, with a response proportion of 69.0%.

The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, and all women provided signed informed consent. Information that was obtained during an in-person interview pertained to the time before diagnosis (for case patients) or before an assigned comparable reference date (for control subjects) and included demographic, reproductive, and lifestyle characteristics. On average, the diagnosis or reference date was 9 months before interview for case patients and 10 months before interview for control subjects. Women were asked to report five categories of symptoms, including nausea; diarrhea or constipation; pelvic or abdominal discomfort, pressure, or pain; bloating or feeling of fullness; and a need to urinate more frequently or urgently than normal. Only symptoms that were present at some point during the year before the diagnosis or reference date, at a frequency of at least daily for at least 1 week, were recorded. For each symptom category, the participant was asked to report the month that the symptoms began and ended, whether she had visited a physician for the symptom, and symptom severity (mild, moderate, or severe). For symptoms that were present during the year before reference but had begun earlier, a specific starting date was not recorded.

Disease stage was examined according to the system of the International Federation of Gynecology and Obstetrics (FIGO). Briefly, the extent of disease is limited to the ovaries in stage I ovarian cancer and to the pelvis in stage II, and disease extends to the peritoneum beyond the pelvis in stage III disease or to distant sites in stage IV disease (10). Using the scheme proposed by Shih and Kurman (11), we categorized histological types of invasive ovarian cancers according to the hypothesized pathways of tumorigenesis, which are characterized by slow progression through stages (type I) or rapid onset and early metastasis (type II). Type I tumors included mucinous, endometrioid, clear cell, well-differentiated serous, and malignant Brenner tumors. Type II tumors were largely moderately and poorly differentiated serous carcinoma, malignant mixed mesodermal tumors, carcinosarcomas, and undifferentiated carcinomas. Because the large majority of serous tumors are considered type II (11), we grouped the 48 serous tumors of unknown grade with type II tumors. We also included 43 tumors with uncommon histologies that were not specifically mentioned by Shih and Kurman (11) as type II tumors, 30 of which were mixed cell adenocarcinoma and only two of which were well differentiated.

Statistical Analysis

We assessed the sensitivity of symptom recognition (as estimated by the proportion of case patients reporting the symptoms of interest) to detect borderline and invasive epithelial ovarian cancer for each of the symptom groups assessed. Also, we assessed the specificity (estimated by the proportion of control subjects without such symptoms) and examined the impact of a recent time of symptom onset on these characteristics. We used Goff's symptom index and of symptoms meeting the consensus criteria to examine their specificity and sensitivity for early- and late-stage invasive disease. We considered the index to be positive when symptoms of pelvic or abdominal pain or bloating or feeling full were present at least daily for at least 1 week, with an onset of less than 12 months before diagnosis or reference date. We considered that the consensus criteria had been fulfilled when symptoms of bloating or feeling full, pelvic or abdominal pain, or urinary urgency or frequency had been present for at least 1 month, with an onset of less than 12 months before diagnosis or reference date.

Calculation of the positive predictive value from case–control data requires an external estimate of the frequency of as-yet undiagnosed cases of disease (12). For this purpose, we used the results of the initial ovarian cancer screening evaluations performed in two screening trials. In one trial, the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial (13), 28816 women who were aged 55–74 years received serum CA-125 testing and/or

CONTEXT AND CAVEATS

Prior knowledge

Use of certain symptoms was encouraged in a recent consensus statement as a way to diagnose ovarian cancer earlier.

Study design

A case–control study was designed in which in-person interviews were conducted with case patients with epithelial ovarian cancer and population-based control subjects. Symptoms assessed as components of a symptom index or consensus recommendations were pelvic or abdominal pain or bloating, feeling full, or urinary urgency or frequency. Positive predictive value was calculated.

Contribution

Symptoms appeared in most case patients within 5 months before diagnosis. Women with early-stage ovarian cancer were somewhat less likely to have symptoms (except nausea) than those with late-stage cancer. The estimated positive predictive value of the symptoms was 0.6%–1.1% overall and less than 0.5% for early-stage disease.

Implications

If symptoms are used as suggested in the consensus statement to trigger medical evaluation for ovarian cancer, then only one of 100 women in the general population with such symptoms is likely to be diagnosed with the disease.

Limitations

Recall bias is always a possibility in case–control studies in that case subjects may be more likely to remember symptoms than control subjects. Patients with very aggressive ovarian cancer may not have been available for interview.

From the Editors

transvaginal ultrasonography; 17 invasive ovarian cancers (four in stage I or II and 13 in stage III or IV) were diagnosed within 12 months after a positive screen. In the other trial (14), 22 000 postmenopausal women, who were older than 45 years, were screened with CA-125 and transabdominal ultrasound; 11 ovarian cancers were identified among women with a positive screen, and eight ovarian cancers were identified among women with a negative screen (three within 1 year and an additional five within 2 years after screening). These values correspond to an estimated overall prevalence in a range of 59.0–63.6 undetected ovarian cancers per 100 000 women after a 12-month follow-up (13,14) to 86.4 undetected ovarian cancers per 100 000 women after a 2-year follow-up (14). The estimated prevalence of undetected early-stage disease was 13.9–22.7 undetected early-stage ovarian cancers per 100 000 women after a 12-month follow-up and 40.9 undetected early-stage ovarian cancers per 100 000 women after a 2-year follow-up. The positive predictive value was calculated according to the following formula:

$$\text{positive predictive value} = p(D)(\text{sensitivity})/\{p(D)(\text{sensitivity}) + [1 - p(D)](1 - \text{specificity})\},$$

where $p(D)$ is the prevalence of undetected disease (12).

Additional goals of our analysis were to compare the types of symptoms in patients with early-stage ovarian cancer (FIGO stage I or II) with those of patients with advanced-stage invasive ovarian cancer (FIGO stage III or IV) and to compare the types of symptoms in patients with invasive tumors that are thought to develop more quickly (type II) with those of patients with invasive tumors that are thought to develop slowly (type I). Age-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by use of unconditional logistic regression; for comparisons among case patients according to disease type (II vs I), we additionally adjusted for stage. (It should be noted that these odds ratios may be interpreted as a relative measure of association but not as a measure of disease risk.) Analyses were conducted with STATA statistical software (version 10.0; STATA Corporation, College Station, TX).

Results

We assessed the presence of one or more symptoms (as nausea, diarrhea or constipation, pelvic or abdominal pain, bloating or feeling full, or urinary frequency or urgency) that lasted for at least 1 week during the year before the diagnosis or reference date among case patients with borderline or invasive epithelial ovarian cancer and control subjects. A total of 977 (74.4%) of control subjects reported no such symptoms; in contrast, 52 (24.0%) case patients with borderline tumors and 90 (15.2%) with invasive tumors reported no such symptoms (Table 1). Among case patients, the symptoms that occurred most commonly were bloating or feeling full (n = 381 [64.1%] and 108 [49.8%] women with invasive or borderline disease, respectively) and pelvic or abdominal pain (n = 362 [60.9%] and 106 [48.8%] women with invasive or borderline disease, respectively). Although a larger proportion of patients with invasive than those with borderline tumors reported each symptom assessed, patients with invasive disease had a more recent onset of a first symptom than did women with borderline disease; for example, 108 (18.2%) of the 594 patients with invasive disease and 21 (9.7%) of the 217 patients with borderline tumors experienced an initial symptom less than 3 months before diagnosis.

Among control subjects, the proportions of women with individual symptom types were generally two to four times lower (equating to improved specificity) when limited to those symptoms that began during the year before the reference date (Table 1). The proportion of control women with symptoms beginning in the latter interval ranged from 2.4% (for nausea) to 4.3% (for urinary urgency or frequency). Differences in symptom reporting between case patients and control subjects were more pronounced when we restricted our analysis to symptoms that began within the past year.

Comparing symptoms starting in the year before diagnosis among women with early-stage invasive cancer with those among women with late-stage invasive cancer, only nausea was more commonly reported by women with early-stage disease (OR = 1.5, 95% CI = 0.9 to 2.6) (Table 2). Other types of symptoms were reported less frequently by women with early-stage disease than by women with late-stage disease, particularly those symptoms that led to a consultation with a physician. The occurrence of some symptoms (diarrhea or constipation, bloating, and abdominal or pelvic pain) rated as severe was also reduced among women with early-stage disease (results not shown). As expected, women with type II invasive tumors were more likely to be diagnosed at a late stage (results not shown). Even after adjusting for disease stage, women with type II invasive tumors were somewhat more likely than those with type I tumors to report pelvic or abdominal pain, bloating or feeling full, and urinary urgency or frequency, and these associations were most evident for those symptoms that led to consultation with a physician.

A positive symptom index occurred among 62.3% of women with early-stage ovarian cancer, among 70.7% of women with late-stage invasive disease, and among 5.1% of control subjects; the corresponding percentages for symptoms that fulfilled the consensus statement criteria were 58.6%, 69.1%, and 6.0% (Table 3). Fewer than 30% of case patients who had a positive index or who fulfilled the consensus criteria, whether diagnosed with early- or late-stage invasive disease, did so more than 5 months before their diagnosis. The index was positive only within the 2 months before diagnosis for 99 (38%) of the 263 women with late-stage disease and a positive index and for 48 (35%) of the 137 women with early-stage disease and a positive index.

The specificities of the symptom index and consensus criteria were slightly higher in women aged 55 years or older, whereas the sensitivity of both measures was reduced (Table 4). Sensitivity ranged from 53.2% (for the consensus criteria in early-stage disease in women aged 55–74 years) to 73.4% (for the symptom index in late-stage disease in women who were younger than 55 years). The positive predictive value (which was based on varying external estimates of ovarian cancer prevalence) ranged from 0.6% to 1.1% for all ages and all stages of invasive disease combined. For stage I or II disease, the positive predictive value ranged from 0.1% to 0.5% among women aged 35–74 years. Relatively small differences were observed when positive predictive values were compared between women who were younger than 55 years and those who were 55 years or older.

Table 1. Occurrence and timing of symptoms among women with borderline and invasive epithelial ovarian tumors and among control subjects*

Symptom	No. of control subjects† (%)	No. of case patients (%)	
		Borderline cancer†	Invasive cancer†
Onset of first reported symptom‡			
None	977 (74.4)	52 (24.0)	90 (15.2)
≥12 mo	209 (15.9)	53 (24.4)	151 (25.4)
6–11 mo	58 (4.4)	42 (19.4)	88 (14.8)
3–5 mo	32 (2.4)	46 (21.2)	154 (25.9)
<3 mo	7 (0.5)	21 (9.7)	108 (18.2)
Missing	30 (2.3)	3 (1.4)	3 (0.5)
Nausea			
None within the last year	1254 (95.5)	193 (88.9)	509 (85.7)
Any within the last year	58 (4.4)	24 (11.1)	83 (14.0)
Started within the last year	31 (2.4)	17 (7.8)	66 (11.1)
Missing	1 (0.1)	0 (0.0)	2 (0.3)
Diarrhea or constipation			
None within the last year	1177 (89.6)	171 (78.8)	391 (65.8)
Any within the last year	132 (10.1)	46 (21.2)	199 (33.5)
Started within the last year	37 (2.8)	31 (14.3)	119 (20.0)
Missing	4 (0.3)	0 (0.0)	4 (0.7)
Pelvic or abdominal pain			
None within the last year	1214 (92.5)	111 (51.2)	232 (39.1)
Any within the last year	96 (7.3)	106 (48.8)	362 (60.9)
Started within the last year	45 (3.4)	82 (37.8)	301 (50.7)
Missing	3 (0.2)	0 (0.0)	0 (0.0)
Bloating or feeling full			
None within the last year	1188 (90.5)	108 (49.8)	209 (35.2)
Any within the last year	122 (9.3)	108 (49.8)	381 (64.1)
Started within the last year	36 (2.7)	82 (37.8)	312 (52.5)
Missing	3 (0.2)	1 (0.5)	4 (0.7)
Urinary frequency or urgency			
None within the last year	1155 (88.0)	134 (61.8)	341 (57.4)
Any within the last year	152 (11.6)	83 (38.2)	250 (42.1)
Started within the last year	57 (4.3)	58 (26.7)	179 (30.1)
Missing	6 (0.5)	0 (0.0)	3 (0.5)

* Symptoms had to have been present at least daily for at least 1 week.

† There were 1313 control subjects, 217 case patients with borderline ovarian cancer, and 594 case patients with invasive ovarian cancer who completed the symptoms portion of the interview.

‡ Onset of first reported symptom was defined as months before diagnosis or reference date (for control subjects).

Discussion

Although symptoms included in the index or consensus recommendations were much more common among women with ovarian cancer, even those with early-stage disease, than among women in general, the typically short interval from symptom onset to diagnosis suggests that rapid progression of most advanced tumors may limit their detection at an earlier stage. On the basis of the calculated positive predictive values of both the symptom index and the consensus criteria, the use of symptoms to trigger medical evaluation for ovarian cancer is likely to result in a diagnosis of the disease in only one of 100 women in the general population with such symptoms.

Strengths of the current study include its large population-based case group and the use of a structured in-person interview to collect symptom information. By focusing on symptoms reported within the year before diagnosis or reference date and examining their time of onset, persistence, and potential to prompt a physician visit, we enhanced the comparability of our results with those of previous studies (1–5,15–23) and with the Ovarian Cancer Symptoms Consensus Statement (6). In addition, we conducted analyses to address the occurrence of symptoms among women with early-stage and/or aggressive histological types of tumors because improved detection of these subtypes may be most likely to improve outcomes of women with ovarian cancer.

This study had several limitations. Recall bias has been suggested as a potential limitation of case–control studies that rely on self-report to assess differences in the occurrence of symptoms among case patients with ovarian cancer and control subjects (1,2) and may influence the results of this study. Case patients may be more likely than control subjects to recall symptoms, or their recall may be influenced by subsequent health status or treatment. Also, as is likely true for previous retrospective studies that relied on self-report (3–5,18,22), women with very rapidly progressive disease may be missing from our study because they could not be interviewed. Our histological categorization of tumors as arising via either type I or type II tumorigenic pathways likely involves some misclassification; this misclassification would serve to mute the observed differences.

Table 2. Association of symptoms with disease stage and type among women with invasive epithelial ovarian cancer*

Symptom (starting in the last year)	Late-stage (III or IV) disease†, No. (%)	Early-stage (I or II) disease†, No. (%)	OR‡ (95% CI)	Type I disease†, No. (%)	Type II disease†, No. (%)	OR‡ (95% CI)
Nausea						
No	334 (89.8)	188 (85.5)	1.0 (ref)	140 (86.4)	383 (88.7)	1.0 (ref)
Yes	35 (9.4)	30 (13.6)	1.5 (0.9 to 2.6)	20 (12.3)	46 (10.7)	1.1 (0.6 to 2.1)
Missing	3 (0.8)	2 (0.9)		2 (1.2)	3 (0.7)	
Consulted physician for this symptom						
No	8 (2.2)	10 (4.5)	1.9 (0.7 to 5.1)	6 (3.7)	12 (2.8)	1.3 (0.4 to 4.3)
Yes	27 (7.3)	20 (9.1)	1.4 (0.8 to 2.6)	14 (8.6)	34 (7.9)	1.0 (0.5 to 2.1)
Diarrhea or constipation						
No	287 (77.2)	182 (82.7)	1.0 (ref)	126 (77.8)	344 (79.6)	1.0 (ref)
Yes	81 (21.8)	37 (16.8)	0.7 (0.4 to 1.1)	34 (21.0)	85 (19.7)	0.7 (0.4 to 1.2)
Missing	4 (1.1)	1 (0.5)		2 (1.2)	3 (0.7)	
Consulted physician for this symptom						
No	20 (5.4)	17 (7.7)	1.2 (0.6 to 2.5)	14 (8.6)	23 (5.3)	0.6 (0.3 to 1.4)
Yes	61 (16.4)	20 (9.1)	0.5 (0.3 to 0.9)	20 (12.3)	62 (14.4)	0.7 (0.4 to 1.4)
Pelvic or abdominal pain or pressure						
No	178 (47.8)	113 (51.4)	1.0 (ref)	91 (56.2)	202 (46.8)	1.0 (ref)
Yes	194 (52.2)	107 (48.6)	0.8 (0.6 to 1.1)	71 (43.8)	230 (53.2)	1.6 (1.1 to 2.5)
Consulted physician for this symptom						
No	19 (5.1)	14 (6.4)	1.1 (0.5 to 2.5)	14 (8.6)	19 (4.4)	0.6 (0.2 to 1.4)
Yes	175 (47.0)	93 (42.3)	0.8 (0.5 to 1.1)	57 (35.2)	211 (48.8)	1.9 (1.2 to 3.0)
Bloating or feeling full						
No	154 (41.4)	123 (55.9)	1.0 (ref)	89 (54.9)	189 (43.8)	1.0 (ref)
Yes	214 (57.5)	97 (44.1)	0.5 (0.4 to 0.7)	73 (45.1)	239 (55.3)	1.3 (0.8 to 1.9)
Missing	4 (1.1)	0 (0.0)		0 (0.0)	4 (0.9)	
Consulted physician for this symptom						
No	53 (14.2)	38 (17.3)	0.8 (0.5 to 1.4)	34 (21.0)	57 (13.2)	0.7 (0.4 to 1.2)
Yes	161 (43.3)	59 (26.8)	0.4 (0.3 to 0.6)	39 (24.1)	182 (42.1)	1.8 (1.1 to 2.9)
Urinary frequency or urgency						
No	255 (68.5)	154 (70.0)	1.0 (ref)	117 (72.2)	294 (68.1)	1.0 (ref)
Yes	113 (30.4)	66 (30.0)	0.9 (0.6 to 1.3)	44 (27.2)	135 (31.3)	1.4 (0.9 to 2.3)
Missing	4 (1.1)	0 (0.0)		1 (0.6)	3 (0.7)	
Consulted physician for this symptom						
No	51 (13.7)	29 (13.2)	0.9 (0.6 to 1.6)	22 (13.6)	58 (13.4)	1.1 (0.6 to 2.0)
Yes	62 (16.7)	35 (15.9)	0.8 (0.5 to 1.3)	21 (13.0)	76 (17.6)	1.8 (1.0 to 3.5)
Missing	0 (0.0)	2 (0.9)		1 (0.6)	1 (0.2)	

* Symptoms had to have been present at least daily for at least 1 week and to have started within the last year. CI = confidence interval; OR = odds ratio.

† In this analysis, there were 372 patients with late-stage disease, 220 with early-stage disease, 162 with type I disease, and 432 with type II disease; stage was unknown for two women, and one woman with invasive disease did not complete the symptoms portion of the interview.

‡ Odds ratios compare women with early-stage disease with women with late-stage disease or compare women with type II disease with women with type I disease and are adjusted for age. Disease type was also adjusted for stage.

Some authors (1) have suggested that a population-based control group may be less informative than a control group of women presenting for primary care because the symptom experience of the latter group of women may provide better information for clinical decision making. However, measurement of the sensitivity, specificity, and positive predictive value of the symptom index or of the consensus statement criteria by use of a population-based comparison is most relevant to a woman who is considering whether her symptoms warrant seeking medical evaluation for ovarian cancer. Our assessment of the symptoms included in the index (pelvic or abdominal discomfort, pressure or pain, or bloating or feeling of fullness, with an onset within the previous year) and consensus statement criteria (as above for the symptom index, with the addition of urinary urgency or frequency) closely replicated those originally proposed (2,6). The length of time that these symptoms had persisted among women who we considered positive was slightly shorter than originally proposed for the symptom index and slightly longer for the consensus criteria. The similarity of the estimated sensitivity, specificity, and positive predictive value of these two measures indicated that these minor differences in symptom duration did not importantly influence our results.

Many studies (1–5,15–23) conducted over the last decade have examined the occurrence of symptoms before diagnosis among women with ovarian cancer. These studies differ in the individual symptoms and symptom groups assessed, the types of populations studied, and the sources of symptom information. Groups of case patients have been population-based samples (3–5,17,20–23), hospital-based samples (3,15,16,19), or convenience samples (1,2,18). In one study (21), women with early-stage (localized) disease were excluded, whereas another study (16) was based entirely on women with early-stage disease. Some studies have examined self-reported symptoms that were assessed retrospectively (3–5,18,22) or prospectively (in case patients, immediately before ovarian surgery) (1,2), and others have gathered information from medical records

Table 3. Occurrence and timing of a positive symptom index or fulfillment of the consensus statement criteria in women with early- and late-stage invasive epithelial ovarian cancer and population-based control subjects*

Symptom measure	No. of control subjects (%)	No. of case patients with early-stage disease (%)	No. of case patients with late-stage disease (%)
Symptom index†			
Negative	1233 (93.9)	83 (37.7)	109 (29.3)
Positive	67 (5.1)	137 (62.3)	263 (70.7)
Missing	13 (1.0)	0 (0.0)	0 (0.0)
Time first positive‡			
6–11 mo	39 (3.0)	35 (15.9)	60 (16.1)
3–5 mo	19 (1.4)	53 (24.1)	104 (28.0)
<3 mo	7 (0.5)	48 (21.8)	99 (26.6)
Missing	2 (0.2)	1 (0.5)	0 (0.0)
Met consensus criteria§			
No	1219 (92.8)	91 (41.4)	114 (30.6)
Yes	79 (6.0)	129 (58.6)	257 (69.1)
Missing	15 (1.1)	0 (0.0)	1 (0.3)
Time first positive‡			
6–11 mo	43 (3.3)	37 (16.8)	73 (19.6)
3–5 mo	27 (2.1)	55 (25.0)	115 (30.9)
<3 mo	9 (0.7)	35 (15.9)	69 (18.5)
Missing	0 (0.0)	2 (0.9)	0 (0.0)

* There were 1313 control subjects, 220 case patients with early-stage disease, and 372 case patients with late-stage disease. Disease stage was unknown for two women with invasive disease, and one woman with invasive disease did not complete the symptoms portion of the interview.

† The symptom index included pelvic or abdominal pain or bloating or feeling full, when present at least daily for at least 1 week and with an onset of less than 12 months before diagnosis or the reference date.

‡ The first time that the symptom index was positive, or consensus criteria were met, before diagnosis or the reference date.

§ Consensus criteria included bloating or feeling full, pelvic or abdominal pain, or urinary urgency or frequency, when present for at least 1 month and with an onset of less than 12 months before diagnosis or the reference date.

(15–17,19) or from medical claims data (20,21,23). Some studies have compared symptoms reported among case patients with those among control subjects without ovarian cancer (1–3,17,21–23), whereas others have made comparisons limited to women with ovarian cancer (4,5,15,16,18,20). Control groups of women without ovarian cancer have included population-based samples (21–23) or clinic-based or convenience samples (1–3).

Despite their differences in design, previous studies have uniformly reported that the overwhelming majority of women with ovarian cancer experience one or more symptoms in the months leading to diagnosis (1–5,15–23), that women with ovarian cancer are more likely than women without cancer to report symptoms in that time interval (1–3,17,21–23), and that the number of symptoms among case patients tends to be greater than that among control subjects (1,2,22), although the duration of symptoms among case patients tends to be shorter than those among control subjects (1,3,21–23). Case patients may also report symptoms that are more severe (1) and occur more frequently or persistently than those in control subjects (1,3). The types of symptoms most commonly reported have included abdominal swelling or mass, bloating, and abdominal or pelvic pain, with gastrointestinal and urinary symptoms also being reported by a substantial number of women.

Some studies have assessed differences in symptoms between women with borderline ovarian cancer and women with invasive ovarian cancer (4,5,15,16,22). Similar to this study, these studies generally indicate that the types of symptoms reported did not clearly distinguish between borderline and invasive disease. In addition (as was also observed in this study), although a higher proportion of women with borderline than invasive tumors did not report symptoms, the duration of symptoms that occurred tended to be longer among women with borderline tumors.

Because early-stage disease accounts for a small proportion of invasive ovarian cancer, data regarding the occurrence of symptoms in this group are limited. Among the studies that have compared women with early- and advanced-stage ovarian cancer (1,3,5,15,17–20,22), one study included borderline tumors among early-stage tumors (17) and several included only small numbers of women with early-stage disease, limiting the comparisons that could be made (eg, ≤50 such women) (1,3,15,17). In various studies, early-stage disease has been defined as confined to the ovaries (17,19) or to the ovaries and pelvis (1,3,5,15,18,22), and one large study examined these subgroups of early-stage disease separately (20). In the aggregate, these previous studies indicate that, although the types of symptoms in women with early-stage disease and in those with late-stage disease are largely overlapping, symptoms of abdominal swelling, distention, or ascites; constipation or diarrhea; and abdominal pain are more likely to be a feature of later-stage disease (5,18–20,22). These findings are consistent with our results and those of Goff et al. (2), who reported that their symptom index (which was based on presence of pelvic or abdominal pain, increased abdominal size or bloating, or difficulty eating or feeling full) was more likely to be positive among women with advanced-stage disease than among women with early-stage disease. Also, the duration of symptoms may be shorter among women with advanced-stage disease than among women with early-stage invasive ovarian cancer (3), although other studies have reported little or no difference in duration of symptoms by stage of invasive disease (5,22). To our knowledge, no studies have

Table 4. Sensitivity, specificity, and positive predictive value of a symptom index and of fulfillment of consensus statement criteria for invasive ovarian cancer

Age group	Sensitivity, % (95% CI)*	Specificity, % (95% CI)*	Range of positive predictive values†, %
All ages (35–74 y)			
Symptom index‡			
All invasive cancers	67.5 (65.4 to 69.6)	94.9 (93.9 to 95.8)	0.77–1.12
Stage I or II	62.3 (59.8 to 64.7)	94.9 (93.7 to 96.0)	0.17–0.49
Stage III or IV	70.7 (68.5 to 72.9)	94.9 (93.8 to 95.9)	0.56–0.62
Consensus criteria§			
All invasive cancers	65.3 (63.1 to 67.4)	93.9 (92.8 to 95.0)	0.63–0.92
Stage I or II	58.6 (56.2 to 61.1)	93.9 (92.7 to 95.1)	0.13–0.39
Stage III or IV	69.3 (67.1 to 71.5)	93.9 (92.8 to 95.1)	0.46–0.52
Age 55–74 y			
Symptom index‡			
All invasive cancers	66.2 (63.4 to 69.0)	95.7 (94.6 to 96.9)	0.91–1.32
Stage I or II	57.5 (54.2 to 60.7)	95.7 (94.4 to 97.1)	0.19–0.55
Stage III or IV	69.4 (66.5 to 72.2)	95.7 (94.5 to 97.0)	0.66–0.74
Consensus criteria§			
All invasive cancers	63.9 (61.0 to 66.7)	95.2 (94.0 to 96.5)	0.78–1.14
Stage I or II	53.2 (49.9 to 56.5)	95.2 (93.8 to 96.6)	0.15–0.45
Stage III or IV	67.7 (64.9 to 70.6)	95.2 (93.9 to 96.5)	0.57–0.64
Age 35–54 y			
Symptom index‡			
All invasive cancers	69.3 (66.1 to 72.6)	93.5 (91.8 to 95.3)	0.63–0.92
Stage I or II	65.9 (62.2 to 69.5)	93.5 (91.7 to 95.4)	0.14–0.42
Stage III or IV	73.4 (70.0 to 76.8)	93.5 (91.7 to 95.4)	0.46–0.51
Consensus criteria§			
All invasive cancers	67.2 (63.9 to 70.5)	92.0 (90.1 to 93.9)	0.50–0.72
Stage I or II	62.7 (59.0 to 66.4)	92.0 (90.0 to 94.1)	0.11–0.32
Stage III or IV	72.4 (68.9 to 75.8)	92.0 (90.0 to 94.1)	0.37–0.41

* Sensitivity and specificity calculations exclude women with missing date for the symptom index or consensus criteria. CI = confidence interval.

† Positive predictive values were calculated by use of prevalence estimates that were based on two ovarian cancer screening trials (13,14).

‡ The symptom index included pelvic or abdominal pain or bloating or feeling full, with the symptom present at least daily for at least 1 week and with an onset of less than 12 months before diagnosis or the reference date.

§ Consensus criteria included bloating or feeling full, pelvic or abdominal pain, or urinary urgency or frequency for at least 1 month and with an onset of less than 12 months before diagnosis or the reference date.

reported a longer symptom duration among women who were diagnosed at a late stage, as might be expected if diagnostic delays were principally responsible for the more common occurrence of symptoms in women with advanced-stage disease.

For symptoms to aid in the detection of early-stage ovarian cancer—particularly detection of aggressive types of ovarian cancers that are currently responsible for high rates of mortality—such symptoms should be present in women with early-stage disease and of sufficient magnitude (eg, severity, frequency, and/or persistence) that their increased recognition can hasten medical evaluation and diagnosis. Also, the natural history of ovarian cancers that are, at present, typically identified at a late stage must include a time period in which the disease is symptomatic but has not yet metastasized. If, as has recently been proposed, some high-grade serous ovarian tumors originate in the fallopian tube (24), such tumors may be already metastatic when identified in the ovary; other type II tumors may spread beyond the ovary early in carcinogenesis (24).

We found that, after adjustment for stage, some symptoms leading to consultation with a physician were more commonly reported by women with type II tumors than by those with type I tumors, perhaps indicating that the perception or severity of symptoms may be greater in women with rapidly progressing tumors than in those with relatively indolent disease. Moreover, symptoms forming the basis of the symptom index and/or consensus criteria were more likely to occur in women with late-stage tumors, consistent with the possibility that these symptoms tend to reflect the presence of advanced disease. Although these findings suggest that the ability of enhanced symptom recognition to increase detection of early-stage invasive ovarian cancer may be limited, improved recognition of symptoms leading to a more rapid detection of advanced cancer may yet allow some improvement in disease outcomes (2).

Goff et al. (2) reported that the sensitivity of the symptom index was 60.0% for early-stage invasive disease and 79.1% for advanced-stage disease (on the basis of 18 early-stage invasive and 41 advanced-stage invasive cancers); these sensitivities are fairly similar to those that we observed in the considerably larger population-based sample examined in this study (ie, 62.3% and 70.7%, respectively). It is possible that the lower sensitivity for late-stage disease that we found in this retrospective study may be attributable to a preferential loss of women with advanced disease and pronounced symptoms if poor health contributed to our inability to interview them. Differences in study size or in the age structure

of the two study populations may also play a role. In the study by Goff et al. (2), the specificity of the symptom index was reported as 90% for women older than 50 years and 86.7% for women younger than 50 years, as based on symptoms reported among women presenting for ultrasound and healthy high-risk women undergoing ovarian cancer screening as participants in an ovarian cancer early detection study. The greater specificity (95.7% in women aged 55 years or older and 93.5% in women younger than 55 years) that we observed in this study likely reflects a lower occurrence of symptoms in a population-based control group.

To our knowledge, no previous studies have calculated the positive predictive value of ovarian cancer symptoms in the general population and have instead relied on proportions or odds ratios to describe the association of symptoms or symptom groupings with the presence of ovarian cancer. Our findings indicate that even pronounced differences in the symptom experience of case patients and control subjects may yield a very low positive predictive value of symptoms to detect ovarian cancer that results chiefly from the rarity of this disease. Although it is possible that our prevalence estimates, which were based on ovarian cancers detected in the initial screening of trial participants (13,14), may underestimate the true prevalence of undetected ovarian cancer in the population, it seems unlikely that, given the aggressive nature of the disease, a substantial number of cancers would remain undetected over the course of 1–2 years of trial follow-up. Estimates of positive predictive value using the ovarian cancer experience in two independent trials (13,14) yielded similar results. The low positive predictive value of symptoms to detect ovarian cancer—particularly at an early stage—argues for a cautious approach to the use of symptom patterns to trigger extensive medical evaluation for ovarian cancer.

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