

Frequency of Symptoms of Ovarian Cancer in Women Presenting to Primary Care Clinics

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OVARIAN CANCER HAS OFTEN been called the “silent killer” because symptoms are not thought to develop until advanced stages when chance of cure is poor. In fact, textbooks in internal medicine, family practice, and even gynecology state that symptoms do not occur until the disease is advanced.¹⁻⁴ However, several retrospective studies have indicated that the majority of patients do have symptoms, although not necessarily gynecologic in nature.⁵⁻⁹ These studies have been criticized because of small numbers of patients included and the retrospective chart analyses used for data collection.

In a previous study, we surveyed 1725 women with ovarian cancer.¹⁰ Surveys were returned from women in 46 states and 4 Canadian provinces. We found that 95% of women with ovarian cancer reported symptoms prior to diagnosis, with the most common being abdominal (77%), gastrointestinal tract (70%), pain (58%), constitutional (50%), urinary (34%), and pelvic (26%). Interestingly, gynecologic symptoms were the least common of the major groups of symptoms. When we evaluated symptoms by stage of disease, we found that in contrast to what is published in most textbooks, 89% of women with stage I/II disease reported symptoms prior to their diagnosis and 97% of those with ad-

Context Women with ovarian cancer frequently report symptoms prior to diagnosis, but distinguishing these symptoms from those that normally occur in women remains problematic.

Objective To compare the frequency, severity, and duration of symptoms between women with ovarian cancer and women presenting to primary care clinics.

Design, Setting, and Patients A prospective case-control study of women who visited 2 primary care clinics (N=1709) and completed an anonymous survey of symptoms experienced over the past year (July 2001-January 2002). Severity of symptoms was rated on a 5-point scale, duration was recorded, and frequency was indicated as number of episodes per month. An identical survey was administered preoperatively to 128 women with a pelvic mass (84 benign and 44 malignant).

Main Outcome Measures Comparison of self-reported symptoms between ovarian cancer patients and women seeking care in primary care clinics.

Results In the clinic population, 72% of women had recurring symptoms with a median number of 2 symptoms. The most common were back pain (45%), fatigue (34%), bloating (27%), constipation (24%), abdominal pain (22%), and urinary symptoms (16%). Comparing ovarian cancer cases to clinic controls resulted in an odds ratio of 7.4 (95% confidence interval [CI], 3.8-14.2) for increased abdominal size; 3.6 (95% CI, 1.8-7.0) for bloating; 2.5 (95% CI, 1.3-4.8) for urinary urgency; and 2.2 (95% CI, 1.2-3.9) for pelvic pain. Women with malignant masses typically experienced symptoms 20 to 30 times per month and had significantly more symptoms of higher severity and more recent onset than women with benign masses or controls. The combination of bloating, increased abdominal size, and urinary symptoms was found in 43% of those with cancer but in only 8% of those presenting to primary care clinics.

Conclusions Symptoms that are more severe or frequent than expected and of recent onset warrant further diagnostic investigation because they are more likely to be associated with both benign and malignant ovarian masses.

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vanced disease reported symptoms. There was no significant difference in the type of symptoms based on early or late-stage disease. Other investigators have also shown that 80% to 90% of women with early stage disease will report symptoms for several months prior to diagnosis.¹¹⁻¹³

Identification of early symptoms may have important clinical implications because 5-year survival for early stage disease is 70% to 90% compared with 20% to 30% for advanced-stage disease.¹⁴ Other important findings from our prior study were that advanced disease was significantly associated with both pa-

tient delays (ignoring symptoms) and physician delays (wrong diagnosis, not performing pelvic examination, not ordering radiographic studies, or not determining serum cancer antigen 125 levels).¹⁰ To date, screening modalities for asymptomatic women, such as serum cancer antigen 125 and trans-

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vaginal ultrasound, have not been shown to be effective in reducing the morbidity or mortality of ovarian cancer.¹⁵ If there were a way for patients and physicians to recognize early symptoms of ovarian cancer, then this may have a favorable impact on survival, even in the absence of accurate screening studies for asymptomatic women.

Another important case-control study was reported by Olson et al¹¹ from Memorial Sloan-Kettering Cancer Center in New York, NY. Women with ovarian cancer (n=168) and controls (n=251) were interviewed about symptoms over the previous 6 months. Those with cancer were interviewed on average 4 to 5 months after diagnosis. These authors found significant differences in symptoms between ovarian cancer patients and controls, with bloating, lack of appetite, abdominal pain, fatigue, urinary frequency, and constipation occurring significantly more frequently in cases than in controls. When the authors looked specifically at patients with early stage disease, they also found that 89% of these patients complained of symptoms prior to diagnosis. For women with early stage disease, bloating was the most common symptom, followed by gastrointestinal tract disturbances.

While both our prior study¹⁰ and Olson et al¹¹ suggest that the majority of women with early and late-stage ovarian cancer have symptoms, both of these studies have weaknesses that need to be addressed. In both studies, women were surveyed or interviewed months to years after their diagnosis, making recall bias a significant issue. Another concern is the issue of selection bias. In particular, the control group in the Olson et al study was not necessarily women seeking medical care—most were contacted by random dialing or were convenience controls. One of the major criticisms of both studies has come from physicians in primary care who point out that many women who present for routine care frequently do complain of symptoms that are typically associated with ovarian cancer but who do not have the disease. There needs to be an appropriate way to dis-

tinguish symptoms that occur commonly from those that are more likely to be associated with ovarian cancer.

The purpose of this study was to identify the frequency, severity, and duration of symptoms typically associated with ovarian cancer in a population of women presenting to primary care clinics. Comparison was made with 128 women with ovarian masses who were surveyed about symptoms prior to surgery and before a cancer or benign diagnosis was established.

METHODS

Approval for this study was obtained from the institutional review boards at the University of Washington and Virginia Mason Medical Center, both in Seattle. Women visiting either of 2 primary care clinics (Family Medicine and Women's Clinic) at the University of Washington were asked to voluntarily fill out an anonymous survey about the symptoms they had experienced over the past year. Participants were given a list of 20 symptoms that are typically associated with ovarian cancer (BOX). These included pain, eating difficulties, abdominal symptoms, bladder symptoms, bowel symptoms, menses, sexual intercourse, and constitutional symptoms. They were asked to rate the severity on a 5-point scale, provide the frequency of symptoms as number of episodes per month, and indicate how long the symptom had been present. In addition, they were surveyed about age, race, parity, education, past medical history, and reason for the clinic visit. Surveys were filled out over a 6-month period (July 2001-January 2002).

A second group of women about to have surgery to remove an ovarian or pelvic mass filled out an identical form regarding their symptoms over the previous year. These were women who presented for gynecology services at both University of Washington and Virginia Mason Medical Center. Surveys were completed prior to surgery and before women were aware of the pathological diagnosis (benign or malignant). Surveys were then correlated with surgical pathological characteristics and

stage of disease. All women signed informed consent.

Statistical analysis was performed using SPSS statistical software (version 10.1, SPSS Inc, Chicago, Ill). Continuous variables were compared using independent tests for 2 groups and analysis of variance with post hoc tests for more than 2 groups. Categorical variables were analyzed with χ^2 (for multiple groups) or Mann-Whitney *U* (for 2 groups) and medians were analyzed using the Kruskal-Wallis *H* test. Correlations were performed with Pearson correlation. $P < .05$ was considered significant.

RESULTS

In the primary care clinics, 1709 women completed the survey over the 6-month period. Approximately 12000 visits by women were made. Because a large percent (30%-50%) were repeat visits within the 6-month period, it was not possible to calculate an accurate response rate to the survey. Patients were instructed not to fill out more than 1 survey. The median age of the patients surveyed was 45 years (range, 15-90 years). A total of 430 patients (25%) made a clinic visit for a general check up, 224 (13%) were visiting only for a mammogram, and 1055 (62%) appointments were for specific problems. The majority of surveys (78%) were returned from patients visiting the Women's Clinic. The racial distribution of respondents was 81% white, 6% Asian, 5% black, 2% Native American, 2% Hispanic, and 4% unknown (not indicated). The highest level of education reported was 8th grade or less for 1%; between 9th and 11th grade, 2%; 12th grade or high school diploma, 12%; 2 years of college, 16%; 4 years of college, 33%; graduate degree, 33%; and unknown (not indicated), 3%. Sixty-four percent of women had been pregnant and 52% had delivered children. Regarding medical history, 12% indicated they had hypertension, 4% diabetes, 3% heart disease, 4% breast cancer, 1% endometrial cancer, 12% thyroid disease, and 7% irritable bowel syndrome (IBS).

Of the women who presented for primary care, 95% reported at least 1 symptom in the past year. The most common symptoms were back pain (60%), fatigue (52%), indigestion (37%), urinary tract problems (35%), constipation (33%), and abdominal pain (28%). The median number of reported symptoms was 4. The median severity of all symptoms was between 2 and 3. In 72% of cases, women had symptoms that occurred at least once per month. The most common recurring symptoms were back pain (45%), fatigue (34%), indigestion (28%), constipation (24%), abdominal pain (22%), and urinary tract problems (16%). The median number of recurring symptoms was 2 and the median severity for all recurring symptoms was between 2 and 3.

Among those who presented to primary care clinics, there was no significant difference in the type of symptom, frequency, severity, or duration between the women who presented to the Family Medicine Clinic compared with the Women's Clinic. Women presenting for a general check up reported significantly fewer symptoms in the past year (3 vs 4; $P = .001$) and fewer recurring symptoms (1 vs 2; $P = .001$) than women presenting for a problem visit. TABLE 1 shows the most common symptoms for those women ($n = 1011$) presenting for a problem visit. The median number of symptoms reported by these women was 4 and the median number of recurrent symptoms was 2. Women with diabetes, thyroid disease, and irritable bowel syndrome (IBS) had significantly more symptoms than other women in the clinic population. Women with IBS were significantly more likely to have fatigue, gastrointestinal tract complaints and abdominal pain compared with other clinic patients ($P < .001$). The median number of symptoms reported by those with IBS was 6 and the median number of recurrent symptoms was 4. Women with diabetes were significantly more likely to have back pain, urinary tract symptoms, constipation, fatigue, and abdominal pain compared with other clinic patients

($P = .02$). Women with hypertension, pulmonary disease, cardiac disease, and prior history of cancer did not report a higher number of symptoms compared with other women in the clinic population.

When we evaluated the impact of age on symptoms, we found that women with no symptoms were significantly more likely to be postmenopausal than premenopausal ($P = .003$). All symptoms were less common as age increased except for urinary tract symptoms. There was a significant decrease in severity of symptoms except for urinary tract symptoms, which significantly increased in severity with age ($P < .001$).

There were 128 women with pelvic masses who completed a survey of symptoms. Most (70%) of these women lived in the western Washington area, which is a population area with approximately 2 million women. The remainder were referred from rural eastern Washington, Idaho, or Alaska (a population of approximately 1 million women). Eighty-four had benign masses ($n = 74$) or tumors of low malignant potential ($n = 10$). In 44 cases, women had malignant epithelial cancers: 11 with early stage disease and 33 with advanced disease. In the women with benign disease, the median age was 55 years and 95% of the women reported symptoms in the prior year; 67% reported recurring symptoms; 8% reported having symptoms for 6 to 12 months; and 19% reported having symptoms for more than 1 year before seeing a clinician. The median number of symptoms was 4 and the median number of recurring symptoms was 2 ($n = 84$). In the group with malignancy, the median age was 55 years and 94% of the women reported symptoms in the prior year with 67% having recurring symptoms. The median number of symptoms was 8 and the median number of recurring symptoms was 4 ($n = 44$). This number was significantly higher than the number of symptoms reported in the clinic, IBS, or benign mass population ($P = .01$). When asked the duration of symp-

Box. Questionnaire on 20 Symptoms Typically Associated With Ovarian Cancer

Have you had any of the following symptoms in the past year? If you had a symptom, please indicate the severity, frequency (number of times per month), and duration of the symptom.

Pain

Pelvic
Abdominal
Back

Eating

Indigestion
Unable to eat normally
Nausea or vomiting
Weight loss

Abdomen

Abdominal bloating
Increased abdomen size
Able to feel abdominal mass

Bladder

Urinary urgency
Frequent urination

Bowels

Constipation
Diarrhea

Menses

Menstrual irregularities
Bleeding after menopause

Intercourse

Pain during intercourse
Bleeding with intercourse

Miscellaneous

Fatigue
Leg swelling
Other
No symptoms

toms before seeking medical attention, 36% had symptoms for 2 months or less; 24%, 2 to 3 months; 3%, 5 to 6 months; 8%, 7 to 12 months; and 14%, more than 1 year.

Table 1 shows a comparison of reported symptoms for women with ovarian cancer and those who presented for problem visits. A separate comparison of women with malignancy and IBS re-

vealed significantly higher percentages in those with malignancy for pelvic pain (41% vs 25%), bloating (70% vs 49%), increased abdominal size (64% vs 32%), and urinary tract symptoms (55% vs 33%). Significantly lower per-

centages of diarrhea (25% vs 66%) and indigestion (36% vs 52%) were found among those with ovarian cancer. TABLE 2 shows the odds ratios (ORs) for symptoms in patients with ovarian cancer compared with the other groups. Women with ovarian cancer were significantly more likely to have pelvic pain, abdominal pain, difficulty eating, bloating, increased abdominal size, and urinary urgency compared with women seeking care in primary care clinics. When compared with women with IBS, the only significant differences were an increase in pelvic pain, bloating, abdominal size, and urinary tract symptoms. A comparison of symptoms between those women with benign and malignant ovarian masses is shown in TABLE 3. Evaluating the combination of bloating, increased abdominal size, and urinary tract symptoms revealed that 43% of women with cancer complained of all 3 symptoms compared with only 10% with benign masses, 13% with IBS, and 8% of the clinic population ($P < .001$). Compared with cancer cases, the ORs for the combination of 3 symptoms were 9.4 for clinic controls, 5.4 for IBS, and 5.3 for benign ovarian mass cases (Table 2). Correlation of symptoms was evaluated for each group of women. In patients with malignancy, bloating was more highly correlated with increased abdominal size and urinary urgency compared with the other groups.

Comparison of severity of symptoms among clinic patients and patients with a benign ovarian mass, ovarian cancer, or IBS revealed that bloating was significantly more severe in those patients with benign and malignant ovarian masses and those with IBS compared with other clinic patients ($P = .001$). When we evaluated symptoms with a severity of 4 or greater (TABLE 4), we found that women with ovarian cancer and IBS are significantly more likely to have more severe symptoms compared with women with benign masses and other clinic patients.

Comparison of median frequency of symptoms is shown in TABLE 5. Women with malignancies have more fre-

Table 1. Women Reporting Various Symptoms in the Past Year

Symptom	No. (%) of Women		P Value
	Ovarian Cancer (n = 44)	Clinic Visit (n = 1011)*	
Type of pain			
Pelvic	18 (41)	264 (26)	.02
Abdominal	22 (50)	301 (30)	.006
Back	15 (34)	617 (61)	.001
Indigestion	16 (36)	374 (37)	.54
Nausea	6 (14)	224 (22)	.15
Bloating	30 (70)	385 (38)	<.001
Increased abdominal size	28 (64)	197 (19)	<.001
Fatigue	27 (61)	548 (54)	.21
Urinary tract	24 (55)	323 (32)	.002
Constipation	22 (50)	363 (36)	.09
Diarrhea	11 (25)	329 (32)	.25
Postmenopausal bleeding	1 (2)	36 (4)	.56
Menstrual irregularity	8 (18)	260 (25)	.22
Combination of symptoms			
3†	19 (43)	81 (8)	<.001
4‡	12 (27)	44 (4)	<.001

*Patients did not have irritable bowel syndrome. Excludes patients who presented for routine checkup or mammogram only.

†Bloating, increased abdominal size, and urinary urgency.

‡Bloating, increased abdominal size, urinary urgency, and constipation.

Table 2. Women With Ovarian Cancer Compared With Those Without Ovarian Cancer

Symptom	OR (95% CI)		
	Cancer vs Benign Ovarian Tumor	Cancer vs Clinic Patients*	Cancer vs IBS Patients
Type of pain			
Pelvic	1.8 (0.8-4.0)	2.2 (1.2-3.9)	2.6 (1.2-5.6)
Abdominal	1.8 (0.8-4.0)	2.3 (1.2-4.4)	0.7 (0.3-1.5)
Back	1.4 (0.6-3.3)	0.4 (0.2-0.7)	0.4 (0.2-0.8)
Difficulty eating	2.5 (0.9-6.8)	2.5 (1.3-5.0)	1.5 (0.7-3.7)
Nausea	0.9 (0.3-2.5)	0.6 (0.2-1.4)	0.6 (0.2-1.4)
Weight loss	0.4 (0.1-1.6)	0.7 (0.2-2.1)	0.8 (0.2-3.2)
Bloating	3.5 (1.5-8.2)	3.6 (1.8-7.0)	3.0 (1.3-6.7)
Increased abdominal size	3.0 (1.3-6.9)	7.4 (3.8-14.2)	4.6 (2.1-10.1)
Abdominal mass	1.4 (0.5-3.4)	5.4 (2.4-12.0)	7.4 (2.3-23.5)
Fatigue	1.1 (0.5-2.6)	1.4 (0.7-2.7)	1.1 (0.5-2.3)
Urinary tract			
Urgency	3.5 (1.6-8.2)	2.5 (1.3-4.8)	2.6 (1.2-5.7)
Frequency	1.9 (0.8-4.3)	1.5 (0.8-2.8)	2.5 (1.2-5.3)
Constipation	3.5 (1.5-8.1)	1.6 (0.9-3.0)	1.0 (0.5-2.2)
Diarrhea	1.6 (0.6-3.9)	0.7 (0.4-1.4)	0.2 (0.1-0.5)
Menstrual irregularity	1.2 (0.5-3.3)	0.7 (0.3-1.4)	0.7 (0.3-1.7)
Combination of symptoms			
3†	5.3 (2.2-12.6)	9.4 (5.0-17.7)	5.4 (2.4-12.2)
4‡	6.2 (2.0-18.8)	8.6 (4.2-17.4)	3.8 (1.5-9.7)

Abbreviations: CI, confidence interval; IBS, irritable bowel syndrome; OR, odds ratio.

*Excludes those patients who presented for routine checkup or mammogram only.

†Bloating, increased abdominal size, and urinary urgency.

‡Bloating, increased abdominal size, urinary urgency, and constipation.

quent pelvic pain, abdominal pain, bloating, fatigue, and urinary tract symptoms compared with other clinic patients. Women with ovarian cancer typically report that symptoms occur every day compared with clinic patients who typically only have symptoms 2 to 3 times per month. Interestingly, women with benign masses have a high frequency of bloating, fatigue, and constipation—each of which occur almost daily.

Evaluation of duration of symptoms is shown in TABLE 6. In general, women with both benign and malignant masses have symptoms of significantly shorter duration. For women with malignancy, the median duration is 6 months or less for all reported symptoms. For women with IBS or other clinic patients, the median duration of symptoms is typically 12 to 24 months.

Secondary analysis was performed in women with early (n=11) vs late-stage (n=33) ovarian malignancy. TABLE 7 shows the comparison of symptom reporting. The small numbers limit the power of the analysis, but most symptoms, including bloating, were seen with equal frequency between the 2 groups. There were also no differences in frequency, severity, or duration; however, larger numbers of cases are required to confirm these findings.

COMMENT

Over the past decade, research efforts have focused on screening and diagnostic protocols to detect ovarian cancer during the early stages. Unfortunately, attaining this goal has remained elusive, and to date no screening test or surveillance strategy has been shown to reduce ovarian cancer mortality.¹⁵ In a study evaluating the efficacy of transvaginal sonographic screening in 14 469 asymptomatic women at risk for ovarian cancer, Van Nagell et al¹⁶ concluded that annual transvaginal ultrasound examinations are associated with a decrease in stage at detection and a decrease in case-specific ovarian cancer mortality. However, in this study there were 57 214 scans performed, and if the 6 patients with borderline and granu-

Table 3. Comparison of Benign and Malignant Ovarian Masses*

Symptom	Total No. (%) of Women	P Value	Median Symptom Severity	No. (%) With Recurring Symptoms	P Value
Pelvic pain					
Benign	31 (37)	.93	3.0	13 (16)	.20
Malignant	18 (41)		4.0	13 (29)	
Abdominal pain					
Benign	35 (42)	.21	3.0	18 (21)	.44
Malignant	22 (50)		4.0	13 (29)	
Bloating					
Benign	41 (49)	.01	3.0	17 (20)	.02
Malignant	30 (70)		3.0	20 (45)	
Increased abdominal size					
Benign	38 (45)	.02	3.0	13 (15)	.33
Malignant	28 (64)		4.0	9 (21)	
Fatigue					
Benign	47 (56)	.63	3.0	21 (25)	.83
Malignant	27 (61)		3.0	11 (24)	
Urinary tract					
Benign	26 (31)	.02	3.0	10 (12)	.34
Malignant	24 (55)		4.0	8 (19)	
Constipation					
Benign	21 (25)	.01	3.0	13 (15)	.17
Malignant	22 (50)		3.0	11 (24)	

*Symptom severity scale is rated on a scale of 1 to 5, with 1 being minimal and 5 being severe.

Table 4. Symptom Severity of 4 or Higher*

Symptom	No. (%) of Women				P Value
	Ovarian Cancer (n = 44)	Benign Ovarian Mass (n = 84)	IBS (n = 109)	Clinic (n = 1600)	
Type of pain					
Pelvic	16 (36)	13 (15)	10 (9)	160 (10)	<.001
Abdominal	10 (23)	9 (11)	22 (21)	121 (7)	<.001
Indigestion	4 (9)	4 (5)	16 (15)	111 (7)	.03
Bloating	20 (45)	12 (14)	19 (17)	123 (8)	<.001
Increased abdominal size	18 (41)	12 (14)	15 (14)	86 (5)	.001
Fatigue	10 (23)	12 (14)	30 (27)	269 (17)	.02
Urinary tract	11 (25)	6 (7)	21 (19)	192 (12)	<.001
Constipation	9 (20)	6 (7)	19 (17)	106 (7)	<.001
Diarrhea	2 (5)	6 (7)	26 (24)	93 (6)	<.001

Abbreviation: IBS, irritable bowel syndrome.

*Symptom severity scale is rated on a scale of 1 to 5, with 1 being minimal and 5 being severe.

Table 5. Median Number of Episodes of Each Symptom per Month

Symptom	Median (IQR)				P Value
	Ovarian Cancer (n = 44)	Benign Ovarian Mass (n = 84)	IBS (n = 109)	Clinic (n = 1600)	
Type of pain					
Pelvic	24 (3-30)	4 (1-29)	2 (1-5)	2 (1-4)	.001
Abdominal	30 (3-30)	7 (4-30)	3 (1-14)	2 (1-5)	<.001
Indigestion	18 (5-30)	9 (3-39)	4 (2-23)	3 (2-9)	.03
Bloating	30 (4-30)	20 (1-30)	4 (1-18)	2 (1-5)	<.001
Fatigue	30 (20-30)	28 (8-30)	25 (4-30)	8 (3-29)	<.001
Urinary tract	30 (23-30)	5 (3-30)	20 (4-30)	12 (3-30)	.02
Constipation	14 (4-30)	25 (6-30)	2 (1-5)	2 (1-5)	<.001
Diarrhea	4 (2-15)	4 (1-30)	3 (1-6)	2 (1-4)	.05

Abbreviations: IBS, irritable bowel syndrome; IQR, interquartile range.

losa cell tumors are excluded, there were only 11 invasive epithelial cancers detected, 5 of which were stage I, 3 stage II, and 3 stage III. This translates into 5200 ultrasounds for each case of invasive cancer detected. A total of 180 women in this study underwent surgery (or 16 surgeries per case of invasive cancer). In another study by Liede et al,¹⁷ screening with transvaginal sonography and cancer antigen 125 was undertaken in Ashkenazi Jewish women at high risk for ovarian cancer. In this

study, the authors concluded that screening in this population was not effective in reducing morbidity or mortality from ovarian or other mullerian cancers. Six of 8 cancers detected during surveillance were stage IIIC. While studies of serum proteomics may hold promise for the future,¹⁸ currently the US Preventive Services Task Force has graded the routine screening of ovarian cancer with a "D" ranking, which is defined as fair evidence to recommend its exclusion in a periodic health exami-

nation.¹⁹ In addition, with limited health care dollars, screening tests need to be cost-effective.

Given that 80% to 90% of women who develop ovarian cancer will not have a worrisome family history, and screening in the general population is not yet effective,¹⁵ it is important for women and practitioners to understand the symptoms of ovarian cancer so that diagnoses can be made as promptly as possible. Theoretically, prompt diagnoses could lead to detection at earlier stages when chance of cure is significantly greater. Even if earlier diagnosis through symptoms does not result in detection of earlier stage disease, it may allow the performance of an optimal cytoreduction in advanced disease. Optimal cytoreduction is associated with cure rates of 30% to 40% compared with 0% to 20% for suboptimal cytoreduction, and median survival of more than 50 months compared with 36 months.²⁰

Our study, like previous ones,^{5-12,21} has shown that symptoms are commonly found in women with ovarian cancer: 94% of patients did have symptoms in the prior year and 67% had recurring symptoms. The symptoms most commonly reported were bloating, increased abdominal size, fatigue, urinary tract symptoms, and pelvic or abdominal pain. These findings are consistent with studies by Olson et al¹¹ and our prior study,¹⁰ both of which found that abdominal and gastrointestinal tract symptoms were the predominant complaints in women with ovarian cancer. Interestingly, many of the women with benign ovarian masses had similar complaints to those with malignant masses. Benign masses have the ability to produce significant gastrointestinal tract and abdominal symptoms. In a study by Vine et al,¹³ the authors compared symptoms in 616 women with ovarian cancer with 151 women with ovarian tumors of low malignant potential. In that study, symptoms were reported prior to diagnosis by 92% of women with invasive cancer and 86% of women with borderline tumors. The most common symp-

Table 6. Median Duration of Each Symptom in Months

Symptom	Median (IQR)				P Value
	Ovarian Cancer (n = 44)	Benign Ovarian Mass (n = 84)	IBS (n = 109)	Clinic (n = 1600)	
Type of pain					
Pelvic	3 (2-9)	2 (1-5)	18 (7-60)	11 (2-18)	.001
Abdominal	4 (1-11)	5 (2-9)	12 (2-111)	11 (3-12)	.03
Indigestion	6 (2-12)	3 (1-12)	12 (4-120)	12 (4-18)	.10
Bloating	3 (1-6)	3 (1-6)	18 (12-165)	12 (4-12)	<.001
Fatigue	3 (1-6)	5 (2-8)	12 (6-48)	12 (6-24)	<.001
Urinary tract	4 (1-10)	5 (1-10)	12 (6-24)	12 (4-24)	.01
Constipation	3 (1-8)	12 (7-12)	24 (12-126)	12 (5-24)	.001
Diarrhea	5 (1-12)	3 (1-7)	21 (12-180)	12 (2-12)	.21

Abbreviations: IBS, irritable bowel syndrome; IQR, interquartile range.

Table 7. Comparison of Symptoms in Women With Early Compared With Late-Stage Ovarian Cancer

Symptom	No. (%) of Women		P Value
	Early Stage (n = 11)*	Late Stage (n = 33)†	
Type of pain			
Pelvic	7 (64)	11 (33)	.09
Abdominal	4 (36)	18 (55)	.49
Back	5 (45)	10 (30)	.46
Thigh	3 (27)	7 (21)	.62
Indigestion	1 (9)	15 (45)	.03
Difficulty eating	1 (9)	12 (36)	.13
Nausea	2 (18)	4 (12)	.63
Weight loss	0	5 (15)	.31
Bloating	6 (55)	24 (73)	.28
Increased abdominal size	6 (55)	22 (67)	.42
Abdominal mass	3 (27)	6 (18)	.66
Fatigue	7 (64)	20 (61)	>.99
Urinary tract			
Urgency	7 (64)	17 (52)	.72
Frequency	5 (45)	15 (45)	>.99
Constipation	5 (45)	17 (52)	.73
Diarrhea	3 (27)	8 (24)	>.99
Menstrual irregularity	3 (27)	5 (15)	.39

*International Federation of Gynecology and Obstetrics stage I/II.

†International Federation of Gynecology and Obstetrics stage III/IV.

toms were pelvic discomfort, bowel irregularities, and urinary tract symptoms. Although the authors did not have access to staging information, one can assume that the majority of borderline tumors were confined to the ovary. Probably any ovarian mass (benign, borderline, or malignant, even if confined to the ovary) has a high likelihood of producing symptoms.

Women who present for care in primary care clinics also commonly have symptoms that can be associated with ovarian cancer. Ninety-five percent have had at least 1 symptom in the prior year and 72% have recurring symptoms. As women aged, almost all symptoms became less frequent and less severe, emphasizing the importance of not attributing symptoms typical of ovarian cancer to the aging process. Not unexpectedly, women who presented for a general check up complained of significantly fewer symptoms than other clinic patients. To some extent this may explain some of the differences in ORs for cases to controls in our study compared with the study by Olson et al. In the Olson et al study, controls were not necessarily women who were visiting a physician; therefore, they were probably not representative of women presenting to primary care clinics for problem visits. If the control group of women in the Olson et al study had fewer complaints it would increase the ORs, which is what was observed. In our study, ORs were 7.4 for increasing abdominal size, 3.6 for bloating, 2.5 for difficulty eating, 2.5 for urinary urgency, and 2.2 for pelvic pain. In the Olson et al study, ORs were 25.3 for bloating; 8.8, difficulty eating; 6.2, abdominal/pelvic pain; and 3.5, urinary tract symptoms. All had significant confidence intervals. Although the ORs are higher in the Olson et al study, it is reassuring to see the reproducibility of their findings in our cases and controls; specifically that bloating, increased abdominal size, pelvic or abdominal pain, difficulty eating, and urinary tract symptoms are all significantly more common in women with ovarian cancer.

Other features that distinguish women with ovarian cancer from those without

include severity and frequency of symptoms. Compared with women in the general clinic population, abdominal pain, pelvic pain, bloating, constipation, and increased abdominal size are significantly more severe in women with ovarian cancer. When compared with women with IBS only, bloating and urinary tract symptoms were more severe in women with ovarian cancer. The number of episodes per month of each symptom was significantly greater for women with ovarian cancer; typically they have a symptom frequency of 15 to 30 times per month. Women with benign tumors have a similar frequency pattern. For women presenting to primary care clinics, symptoms typically occur 2 to 3 times per month, often with menses. Even women with IBS typically have symptoms 2 to 3 times per month with the exception of fatigue, diarrhea, and urinary tract symptoms. Olson et al¹¹ also asked women if they experienced their symptoms continuously or intermittently. Olson et al found that bloating, fullness, and abdominal pressure were significantly more likely to be experienced continuously by women with cancer compared with controls (62% vs 36%).

Duration of symptoms is another area that we find significant differences between women with benign or malignant ovarian masses compared with those women who present to primary care clinics. In general, women with ovarian masses will have symptoms with a median duration of 3 to 6 months and those with IBS or other patients presenting to primary care clinics will have symptoms for a median of 12 months to 2 years. The study by Olson et al¹¹ also found that symptoms of short duration were significantly associated with ovarian cancer compared with controls. In the study by Vine et al,¹³ median duration of symptoms for women with invasive cancer was 2 to 4 months compared with 4 to 6 months for women with borderline tumors. These differences were significantly different. In a study by Eltabbakh et al,¹² median duration of symptoms for women with invasive tumors was 3.4 months and borderline tumors was 8.0 months ($P=.03$).

Another important difference between women with ovarian cancer and those without is the number of symptoms that women experience. In our study, the median number of symptoms among women with ovarian cancer was 8 compared with 4 in the clinic population, and the median number of recurring symptoms was 4 compared with 2, respectively ($P=.01$). We also found significant differences in the median number of symptoms between those with benign tumors compared with malignant tumors. The median number of symptoms in women with benign tumors was 4 compared with 8 in patients with ovarian cancer, and the median number of recurring symptoms was 2 compared with 4. Olson et al¹¹ also found significant differences between cases and controls. Women with ovarian cancer had a mean (SD) of 3.0 (1.8) symptoms vs 0.8 (1.3) for the control group ($P<.001$). Eltabbakh et al¹² found no statistical difference in number of symptoms between those with stage I/II invasive ovarian cancer compared with borderline tumors. However, in that study, symptom information was abstracted retrospectively from chart reviews. In our study, the combination of bloating, increased abdominal size, and urinary tract symptoms was seen in 43% of women with ovarian cancer compared with only 8% of those presenting to the primary care clinic, emphasizing the importance of coexisting symptoms when trying to distinguish symptoms typical of malignancy compared with those without. While ORs for combined symptoms were somewhat better than for single symptoms, ORs were not additive, indicating codependence of symptoms.

While our current study did find that women who present to primary care clinics frequently have vague symptoms that can be associated with ovarian cancer, the important difference is that these symptoms are less severe and less frequent when compared with women with ovarian cancer. Typically, symptoms occur 2 to 3 times per month and are often associated with menses, which may explain why these vague

symptoms become less common and less severe as women age. In addition, women with ovarian cancer typically have symptoms of recent onset and have multiple symptoms that coexist.

This study adds further evidence that ovarian cancer is not a silent disease. It is important to emphasize that the majority of women who have symptoms from our list of 20 complaints will not have ovarian cancer. Nonetheless, this initial study gives better definition of symptoms typically associated

with ovarian cancer, providing valuable information for both women and their clinicians. Symptoms that are more severe, more frequent than expected, and of more recent onset warrant further diagnostic investigation. These symptoms are more likely to be associated with ovarian masses, many of which may be malignant.

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Study concept and design: Goff, Melancon, Muntz.
Acquisition of data: Goff, Melancon, Muntz.
Analysis and interpretation of data: Goff, Mandel, Muntz.

Drafting of the manuscript: Goff, Melancon, Muntz.
Critical revision of the manuscript for important intellectual content: Goff, Mandel, Muntz.

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