Symptoms Associated With Ovarian Cancer

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Abstract: Over the past decade there has been considerable evidence that women with ovarian cancer do have recognizable symptoms before diagnosis. The most common symptoms associated with ovarian cancer are abdominal bloating, increased abdominal size, pelvic pain, abdominal pain, feeling full quickly, and difficulty eating. Some studies also suggest that urinary symptoms are frequently present. When these symptoms occur more than 12 times per month and are of new onset, then ovarian cancer should be considered as a possibility. It is important for women and practitioners to be aware that ovarian cancer is not a "silent disease."
Key words: symptoms, ovarian cancer, screening, CA125, transvaginal ultrasound

The World Health Organization classifies ovarian cancer as a disease that would likely benefit from screening due to the substantial improvement in survival if disease is detected early.[1,2] To date, no studies have shown that screening either high-risk populations or the general population has an impact on the morbidity or mortality of the disease. Although there is active research in early detection, especially with biomarkers, currently in 2011 no national organizations or expert consensus panels recommend screening for the women at average risk. In fact, the American Congress of Obstetricians

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and Gynecologists recommends against population-based screening for ovarian cancer,[3] and the US Preventative Services Task Force has assigned screening for ovarian cancer a "D" grade.[4] This indicates that there is fair evidence to recommend its exclusion from periodic health examinations. The rationale is that more women are harmed from the false positives of screening than benefit from early detection.

In the absence of reliable screening methods for ovarian cancer, researchers have been interested in prevention with risk-reducing surgery for those with hereditary predispositions for developing ovarian/fallopian tube cancer and alternative methods of early detection in those without a significant family history. Sporadic ovarian cancer accounts for approximately 85% of the cases of this disease. Historically, ovarian cancer had always been called "the silent killer" because symptoms were not thought to develop until advanced stages, when chances of cure were very poor. Until recently most text books in internal medicine, family practice, and obstetrics and gynecology stated that ovarian cancer was an asymptomatic disease. However, new research has shown that symptom identification is important in the diagnosis of this disease.

In the 1980s and 1990s there were several retrospective studies that examined symptoms in women with ovarian cancer.[5–7] All these studies concluded that ovarian cancer patients did have symptoms before diagnosis, although the symptoms were often vague and not necessarily gynecologic in nature. Although there was significant agreement across these studies, they were criticized because of small numbers and retrospective chart analysis for data collection.

In 2000, a large survey of 1725 women with ovarian cancer from the United States and Canada was published evaluating the type of symptoms, if any, that women experienced before diagnosis and if there were any delays in diagnosis.[8] Although the study was retrospective, the findings were significant in that 95% of women with ovarian cancer developed symptoms an average of 3 to 6 months before seeing a physician. The most common symptoms were abdominal (77%), gastrointestinal (70%), pain (58%), constitutional (50%), urinary (34%), and pelvic (26%). Interestingly, gynecologic symptoms were the least common (Table 1). Evaluation by stage revealed that in patients with early-stage disease (having cure rates of 70% to 90%), 89% complained of symptoms before diagnosis. Type of symptoms did not vary based on stage.

Survey respondents also reported significant delays in diagnosis.[8] Both physician-related and patient-related delays in diagnosis were common. Physicians commonly diagnosed women with irritable bowel syndrome, stress, gastritis, or depression months before the diagnosis of ovarian cancer. In this study, 30% of women were treated with a prescription medication for another condition within months preceding their ovarian cancer diagnosis. Physician misdiagnosis was associated with more advanced stage of disease. In addition, patients frequently did not recognize their symptoms as something that could be serious. In this

TABLE 1. Frequency of Symptoms in Ovarian Cancer

Symptoms	Frequency (%)
None	5
Increased abdominal size	61
Bloating	57
Fatigue	47
Abdominal pain	36
Indigestion	31
Urinary frequency	27
Pelvic pain	26
Constipation	25
Back pain	23
Pain with intercourse	17
Unable to eat normally	16
Palpable mass	14
Vaginal bleeding	13
Weight loss	11
Nausea	9
Bleeding with intercourse	3
Diarrhea	1
Deep venous thrombosis	1

study women who said they ignored their symptoms were significantly more likely to be diagnosed with advanced-stage disease as compared with those who felt they did not ignore their symptoms. However, although this was an important study there were significant weaknesses in the study design. First, there were no controls for comparison and second there were unavoidable issues of recall bias.

In 2001, a case-control study from Memorial Sloan-Kettering Cancer Center was published.[9] Women with ovarian cancer (n = 168) and controls (n = 251) were interviewed for symptoms experienced during the preceding 6 months. The authors found that ovarian cancer patients were significantly more likely to complain of bloating, lack of appetite, abdominal pain, fatigue, urinary frequency, and constipation than controls (Table 2). In this study, 89% of women with early-stage disease also complained of symptoms before diagnosis, and there was no significant difference in the symptoms reported between those with early-stage versus late-stage disease. When the authors compared symptoms in women with early-stage

TABLE 2. Comparison of Symptoms Between Ovarian Cancer Cases and Controls OR With 95% CI

	OR (95% CI)	
Symptoms	Olson et al[9]	Goff et al[10]
Bloating	25.3 (15.5-40.9)	3.6 (1.8-2.0)
Difficulty eating/lack of appetite	8.8 (4.3-18.2)	2.5 (1.3-5.0)
Abdominal pain	6.2 (4.0-9.6)	2.3 (1.2-4.4)
Urinary symptoms	3.5 (2.2-5.7)	2.5 (1.3-4.8)
Constipation	3.5 (2.0-6.3)	1.6 (0.7-1.4)
Fatigue	2.9 (2.5-6.1)	1.4 (0.7-2.7)

CI indicates confidence interval; OR, odds ratio.

disease to controls, the odds ratios (OR) were still significant: bloating [OR, 19.2; 95% confidence interval (CI), 9.9-37.5], abdominal pain (OR, 5.5; 95% CI, 2.8-10.8), constipation (OR, 5.5; 95% CI, 2.5-12.0).

One of the concerns regarding the Memorial study was that the controls were not necessarily women visiting a physician's office and therefore, may not represent a group that would likely have many complaints. To address this concern, researchers at the University of Washington evaluated symptoms typical of ovarian cancer in over 1700 women presenting to a large primary care clinic.[10] Women were surveyed about the types of symptoms they had experienced over the prior year. In addition, they provided information about the frequency, severity, and duration of symptoms. The clinic patients were then compared as controls to a group of 128 women with pelvic masses who filled out an identical survey before surgery and before they knew whether or not their mass was malignant. Symptoms such as bloating, increased abdominal size, urinary symptoms, and pelvic and abdominal pain were found significantly more frequently in women with ovarian cancer than in those presenting to primary care clinics. The ORs for symptoms for cases as compared with controls are shown in Table 2. One of the potential reasons that the ORs are so much lower in the Goff et al's[10] study is that the control group used were patients visiting their primary care physician for a problem. In addition, 72% of the clinic population did have recurring symptoms, with the most common being back pain, fatigue, and constipation. Interestingly, as women got older most symptoms, except urinary symptoms, were less common and less severe.

The study from the University of Washington also explored the presentation of symptoms in cancer patients versus controls.[10] Cancer patients typically reported that their symptoms occurred 20 to 30 times per month as compared with 2 to 3 times for the clinic population. The severity of symptoms was also significantly higher in cancer patients and of more recent onset. For instance, duration of symptoms was usually < 3 to 6 months for cancer patients as compared with a year or more for the clinic controls. The authors also noted that 44% of women with ovarian cancer had a triad of bloating, increased abdominal size, and urinary urgency, as compared with only 8% of clinic controls. Therefore, although the types of symptoms that women with ovarian cancer experience are vague and frequently reported by women presenting to primary care clinics, the important distinction between cases and controls seems to be in the frequency, severity, and duration of the symptoms. Researchers from other institutions across the United States and in other countries have found remarkably similar findings.[11–14] In addition, large population-based studies have identified the majority of ovarian cancer patients as experiencing significant symptoms before diagnosis.[15–20]

The investigators from the University of Washington did a follow-up case-control study to establish a symptom index that might be useful in the early diagnosis of ovarian cancer.[21] In this study, there

were 149 women with ovarian cancer who were surveyed for symptoms before surgical exploration, and controls consisted of 255 women in an ovarian cancer screening program and 233 women who were referred for pelvic ultrasound. Logistic regression was used to determine which factors independently predicted ovarian cancer in an exploratory group, and then sensitivity and specificity were tested in a confirmatory group. The symptom index that was most predictive of a woman having ovarian cancer was having any 1 of the 6 symptoms (bloating, increased abdominal size, difficulty eating, feeling full quickly, abdominal, or pelvic pain), which occurred more than 12 times per month and were present for less than a year. The overall sensitivity and specificity was 70% and 86%, respectively. The sensitivity for detecting early-stage disease was 57% and 80% for advanced-stage disease. Retrospective analysis of the symptom index in the 1700 women who had been screened in the primary care clinic revealed that only 2.6% tested positive. These investigators are currently conducting a large clinical trial using symptom-triggered screening for ovarian cancer. Women who screen positive on a symptom index (Fig. 1) are referred for testing with CA125 and transvaginal ultrasound (TVS). Although the sensitivity of the symptom index is likely to be a significant weakness, symptom identification may be a low-cost method to improve rates of early detection in the general population, a group for which no screening test exists nor is recommended.

Other investigators have found slightly different patterns of symptom presentation in women with early-staged versus advanced-staged disease. In a population-based case-control study evaluating 432 women

Are you currently experiencing any of the following symptoms? Check the box Yes or No. If yes, also check the box for number of days per month and the box for the number of moths you experienced each symptom.

Symptom Study Index for Ovarian Masses

Symptom	Have you had this symptom?		How many <u>days</u> per month did you experience this symptom?			How long did this symptom persist? (months)			
	No	Yes	<1-5	5–12	≥ 13	<1	1–6	6-12	≥12
Pain									
Abdominal/Pelvic Pain	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8
Eating									
Feeling full quickly	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8
Unable to eat normally	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8
Abdomen									
Abdominal bloating or Increased abdomen size	□ 0	□ 1	□ 2	□ 3	□ 4	□ 5	□ 6	□ 7	□ 8
□ No symptoms									

FIGURE 1. Symptom Index Questionnaire

with invasive ovarian cancer to 491 matched controls, symptom data were collected with interviewer-administered questionnaires. The predictive ability of symptoms was evaluated by comparing the area under the receiver operating curves (ROC).[20] These investigators found that abdominal pain (ROC = 0.817), distended abdomen (ROC = 0.83), vaginal bleeding not associated with periods (ROC = 0.88), and palpable abdominal mass (ROC = 0.88) were significantly predictive of localized disease. The combination of this symptom index has a sensitivity of 74% with a specificity of 71%. Urinary symptoms had low predictive probability. The combination of fatigue/loss of appetite and bowel symptoms was predictive of advanced-stage disease. Researchers from CDC evaluated the SEER Medicare database for diagnosis and procedure codes in 3250 women over age 65 without cancer.[17] They found in a sample without recall bias that 81% of women had visits for gastrointestinal, urinary, or gynecologic symptoms before diagnosis. Women presenting with gastrointestinal symptoms were more likely to have later-stage disease and longer time to key diagnostic tests than those with gynecologic symptoms.

One of the main concerns about symptom reporting is the issue of recall bias[22]; however, there have been several case-control studies evaluating chart notes and claims data of ovarian cancer patients before their diagnosis.[16,17,23] These studies confirm that women with ovarian cancer are significantly more likely than controls to have target symptoms 3 to 6 months before diagnosis. Smith et al[16] evaluated the SEER Medicare database for 1985 ovarian cancer patients, 6024 breast cancer patients, and 10,941 noncancer patients. The prevalence of ICD-9 diagnosis codes was compared before the diagnosis date or reference date for noncancer patients. Ovarian cancer patients were significantly more likely to have visits for target symptoms, including abdominal pain, abdominal swelling, and gastrointestinal complaints within 6 months before diagnosis. Hamilton et al[23] performed a chart review of 212 ovarian cancer patients and 1060 controls and found that 85% of cases had 1 of the 7 ovarian cancer symptoms documented in the medical records before diagnosis as compared with 15% of controls. Abdominal distension, urinary frequency, and abdominal pain were significantly associated with ovarian cancer even at 6 months before diagnosis. The positive predictive value of abdominal bloating was 2.5% in this study.

Other investigators have evaluated the University of Washington symptom index retrospectively and have found poor performance. In a study by Pavlik et al,[24] only 6 of the 30 patients (20%) who had undergone surgery for ovarian cancer had a positive symptom index. The authors did not provide information as to how long after surgery symptom information was collected. Rossing et al[19] also retrospectively surveyed women for symptoms before diagnosis and compared this to age-matched controls. In this study, women were surveyed on an average of 9 months after diagnosis. In this study, the symptom index was positive in 62.3% of women with early-stage disease and 70.7% of those with advanced-stage disease, but only 30% of women with a positive symptom index became positive more than 5 months before their diagnosis. In addition, the authors retrospectively calculated a positive predictive value and found it to be low, approximately 1%. Because of the low positive predictive value the authors argue for a cautious approach to the use of symptoms to trigger an extensive medical evaluation for ovarian cancer. The low estimates of positive predictive values are not surprising given the frequency of these symptoms in the general population and the low incidence of ovarian cancer (40 per 100,000 women over age 50), but it does not mean that these symptoms should be ignored.[25]

From a practical perspective, until we have a cost-effective screening test that

can be used in women at average risk of ovarian cancer, it is important for women and practitioners to be aware of the symptoms associated with ovarian cancer. Symptoms most typical of ovarian cancer include bloating, abdominal or pelvic pain, and difficulty eating. In some studies urinary symptoms are also a common presenting symptom. When these symptoms occur more than 12 times per month and are of recent onset, then ovarian cancer should be considered as a possibility. Although most women who have these symptoms will not have ovarian cancer, it is important that providers include ovarian cancer in their differential diagnosis. The first step in evaluating these types of symptoms is to perform a thorough history and examination, including a pelvic and rectovaginal examination, to evaluate for the possibility of an ovarian abnormality as well as other conditions. Imaging such as transvaginal ultrasound, blood tests such as CA125 or additional diagnostic tests will be determined by the initial clinical evaluation. Critics have raised concerns that evaluation of symptoms will lead to unnecessary surgery; however, a recent clinical trial of over 2000 women evaluated with symptoms screening followed by symptom-triggered transvaginal ultrasound and CA125 found that none of the screened patients underwent a laparotomy or even laparoscopy because of enrollment in a symptom-screening program.[26]

Ultimately, the timely diagnosis of ovarian cancer will rely on clinical judgment and careful analysis of presenting symptoms within the context of a thoughtful dialogue between the patient and her physician.[22] Through research from the past decade, we now understand that there are patterns associated with ovarian cancer. We now know that ovarian cancer is not a "silent disease," but clinicians must still listen carefully to avoid potentially harmful delays in diagnosis.

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