Ovarian Cancer
Screening and Early Detection

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KEYWORDS

• Diagnosis • Early detection • Screening • Symptoms

KEY POINTS

- Screening for ovarian cancer is not recommended for women of average risk.
- Using biomarkers with secondary screening by transvaginal ultrasound show the most promise for effective screening in research studies.
- Most women with ovarian cancer will have symptoms and this disease should no longer be considered "silent".
- Currently the best method for early diagnosis is for both patients and practitioners to have a high index of suspicion when symptoms are present.
- The most common symptoms of ovarian cancer include bloating, abdominal or pelvic pain, feeling full quickly or difficulty eating and urinary symptoms. Symptoms that are relatively new to a patient and occur about 50% of the month are the symptoms to be most concerned about.

SCREENING

In 1994 the US National Institutes of Health convened a consensus conference for the management of ovarian cancer.[1] At that time, the recommendation was to obtain a family history and offer screening to those who had 2 or more affected family members (ovarian cancer or premenopausal breast cancer). However, no guidance was given as to what screening modality should be used or how frequently. Screening women without a significant family history was not recommended.[1] Unfortunately, almost 20 years later, there still are no recommended screening tests for average risk women. For women at elevated risk secondary to family history consistent with BRCA1, BRCA2, or the Lynch syndrome, genetic testing is recommended because screening has not been shown to reduce the morbidity or mortality of ovarian cancer in these patients.[2] Identifying women with deleterious mutations allows practitioners

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to offer counseling and possible interventions to those at elevated risk of developing ovarian cancer.[3]

In 2012, no organization recommends screening average risk women. The American Congress of Obstetricians and Gynecologists recommends against screening for ovarian cancer in the general population.[4] The US Preventative Services Task Force gives ovarian cancer screening a grade "D" recommendation, which indicates this should be eliminated from a periodic health examination because more women are harmed by the false–positive results than helped by early detection.[5] The Society of Gynecologic Oncologists also does not advocate screening for ovarian cancer outside of clinical trials.[2] The US Preventative Services Task Force does give a grade "B" recommendation for genetic counseling and testing of women with a pedigree consistent with a familial mutation that would increase the risk of ovarian and other malignancies.[3] Those found to have mutations can be offered risk-reducing surgery, which dramatically lowers the risk of developing ovarian, fallopian tube, or primary peritoneal cancers.

There are several challenges in developing screening strategies in ovarian cancer.[6] First, unlike breast cancer or cervical cancer, there is no defined in situ lesion. Some recent evidence suggests that, for high-grade serous tumors associated with BRCA1 or BRCA2 mutations, the fallopian tube may be the initial site of a precursor lesion.[7] These results are preliminary and it is unclear if the same association between in situ lesions in fallopian tube and ovarian cancer will be found in women without these mutations. Another challenge is that a major operative procedure (laparotomy or laparoscopy) is usually required for diagnosis.[6,8] Given that there is a low, but definite risk, of morbidity from these types of surgical procedures, any screening strategy for ovarian cancer needs to ensure that the morbidity and possible mortality from false-positive screens will not outweigh the possible benefits of early detection.

The risk of false-positive screens with ovarian cancer screening is a significant concern. This is a major challenge to overcome in the effort to design effective screening programs. The main issue is that the incidence of ovarian cancer in women over age 50 is only 40/100,000.[9] That means even with a perfect screening test, 2500 screens are needed to detect 1 case of ovarian cancer. It also means that if a screening test has only a 1% false-positive rate (sensitivity of 99%), then of every 2500 women screened 25 would have false-positive tests yielding a positive predictive value (PPV) of 4%. In general, it has been accepted that a screening test that results in a major surgical procedure should have a PPV of at least 10%. That means for every case of cancer detected there would be no more than 10 "unnecessary" surgeries (false positives). With an incidence of 40 in 100,000, a screening test would need a specificity of 99.6% or a false-positive rate of less than 0.4% to have a PPV of 10% or higher. The final challenge with ovarian cancer screening is developing a screening test that is not only effective, but also reasonably inexpensive. Because 2500 women need to be screened to detect a single ovarian cancer, the cost must be affordable, and the test readily available and acceptable to patients.

Two large, prospective, randomized screening trials for ovarian cancer have recently been conducted in average-risk women.[10,11] The results of the Prostate Lung Colorectal and Ovarian Cancer screening trial have been reported over the last decade.[10,12] There were 78,232 women between the ages of 55 and 74 who were enrolled between 1993 and 2001. Women randomly assigned to screening underwent annual transvaginal ultrasonography (TVS) for 4 years and annual CA125 for 6 years. Controls consisted of women who were assigned to receive routine care. For the group randomized to screening, any abnormalities and decisions about surgery were managed by the patient's physician according to standard of care. In the initial

Table 1
Pathologic results from the United Kingdom collaborative trial of ovarian cancer screening prevalence screen

Participants Undergoing Surgery	MMS	TVS
n (%)	97 (0.2)	845 (1.8)
Pathology		
Benign	40	732
LMP*	8	20
Primary ovary/fallopian tube	34	5
Metastatic	3	5
Early stage disease	47.1%	50.0%

Abbreviation: LMP, low malignant potential tumor.
Data from Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Lancet Oncol 2009;10:327–40.

prevalence screen, the investigators found that CA125 was elevated in 1.5% of the population and TVS was abnormal in 4.7% of the population. The PPV of the screening tests was 3.7% and 1%, respectively. Over a 4-year period, compliance with screening dropped to 77.6%. The overall ratio of surgeries to screen detected cancers was 19.5:1 and 72% of the screen detected cancers were late stage.[12]

In June 2011, the final results of the effect of screening on ovarian cancer mortality were reported for the Prostate Lung Colorectal and Ovarian Cancer trial.[10] The median follow-up of participants was 12.4 years. Ovarian cancer was diagnosed in 212 women in the screened group and 176 in the control group. There were 118 deaths caused by ovarian cancer in the screened group compared with 100 deaths among the controls. Screening with an annual TVS and CA125 did not reduce ovarian cancer mortality. In addition, of the 3285 women with a false-positive result, 1080 underwent surgery and 163 (15%) experienced at least 1 serious complication. This confirms that cancer screening can lead to unintended harm.

More encouraging results have been found in the United Kingdom Collaborative Trial of Ovarian Cancer Screening.[11] Results from the prevalence screen were reported in 2009. Between 2001 and 2005, a total of 202,632 postmenopausal women aged 50 to 74 years were randomly assigned to no screening (control; n = 101,359), annual CA125 screening (interpreted using an unpublished risk of ovarian cancer algorithm) with TVS as a secondary screen for those with abnormal CA125s (multimodality screening [MMS]; n = 50,640) or annual screening with TVS (TVS; n = 50,639). Of those in the MMS group, 97 (0.2%) underwent surgery owing to the screening process compared with 845 (1.8%) in the TVS group. Pathologic evaluation is shown in **Table 1**. In both screening groups, approximately 50% of ovarian cancers were diagnosed in the early stage. In the group screened with TVS there were 732 surgical procedures performed for benign conditions, indicating a relatively high false-positive rate of TVS compared with the MMS. For primary invasive epithelial and tubal cancers the sensitivity, specificity and PPVs were 89.5%, 99.8%, and 35.1% for MMS and 75.0%, 98.2%, and 2.8% for TVS, respectively. There was a significant difference in specificity ($P<.0001$), but not sensitivity between the 2 groups. Because a PPV of 10% is considered the minimal acceptable value for a screening test that would lead to an invasive surgical procedure, then a huge advantage of the MMS

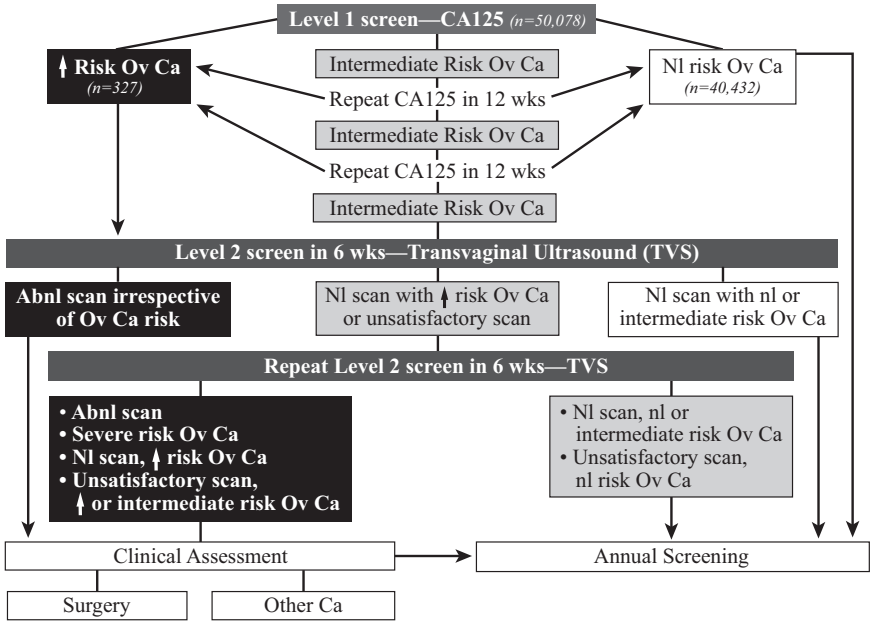

Fig. 1. UKCTOS Pathologic Results from Prevalence Screen. (*Adapted from* Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Lancet Oncol 2009;10:327–40; with permission.)

process is that with a PPV of 35.1, only 2.8 surgeries would be performed for each case of ovarian cancer detected. In contrast, for the TVS group, a PPV of 2.8% means that 35.2 surgeries would be performed for each case of cancer. Although the preliminary results are encouraging, final analysis comparing cancer mortality between screened and controls will need to be performed to assess efficacy. In addition, the screening algorithm for the MMS arm is quite complex and may be difficult to replicate outside a clinical trial (**Fig. 1**).

A screening algorithm similar to the UK MMS group was evaluated by researchers at the M.D. Anderson Cancer Center.[13] In a single-arm study, investigators screened women for ovarian cancer using CA125 levels with a Risk of Ovarian Cancer Algorithm (ROCA) followed by secondary screening with additional CA125 or TVS if patients were intermediate or high risk. There were 3238 postmenopausal women who participated over 8 years. After each CA125 level drawn, women were triaged based on risk into these categories: Annual CA125 (low risk), repeat CA125 in 3 months (intermediate risk), or TVS and referred to a gynecologic oncologist (high risk). Surgery was performed at the discretion of the gynecologic oncologist. Eight women underwent surgery as a result of screening, with 3 invasive ovarian cancers, 2 borderline ovarian cancers, and 3 benign ovarian tumors. All 3 ovarian cancers were early stage. The specificity of the ROCA was 99.7% and PPV was 37.5%.

It is clear from these studies that using TVS as a secondary screening tool significantly improved both the specificity as well as PPV when detecting ovarian cancer.[14] There has been 1 large study of TVS as a primary screen in over 25,000 women from the University of Kentucky. Over an 18-year period, asymptomatic

women over age 50 and women over age 25 with a significant family history were offered TVS for screening. In this study, 364 women underwent surgery (1.4%). TVS had a sensitivity of 85%, specificity of 98.7%, and a PPV of 14.0%. However, this center has special expertise in TVS and screening for ovarian cancer; therefore, these results have not been replicated by other investigators. Specifically, in the Prostate Lung Colorectal and Ovarian Cancer trial, where TVS was performed at multiple centers in over 39,000 women, the PPV was only 1.0%.[12] For a screening regimen to have adequate specificity to prevent potential harm form unnecessary surgery, TVS will most likely need to be utilized as a secondary screen after biomarker evaluation.

Given that the prevalence of ovarian cancer is significantly higher among women with a strong family history or know genetic mutation (BRCA1, BRCA2, mismatch repair genes), hopes were that screening strategies may be more successful in this high-risk group than in the general population. Unfortunately, this hope has not been realized.[15] One of the initial large studies came from the National Ovarian Cancer Early Detection Program.[16] Women at elevated risk of ovarian cancer based on family history, but not genetic testing, were screened every 6 months with TVS. Women had to have a normal TVS to enter the trial. There were 4526 women enrolled in the study. A total of 49 women underwent invasive operative procedures and 12 gynecologic malignancies were diagnosed in women with a normal TVS 12 and 6 months before their diagnosis. All 10 ovarian and fallopian tube cancers were detected in advanced stages. The authors concluded that TVS, even every 6 months, had limited value as a screening test in women at increased risk for disease.

Other studies have focused specifically on women with BRCA1 and BRCA2 mutations. Annual surveillance using both CA125 and TVS has not been associated with earlier stage diagnosis.[17–19] The vast majority of women with mutations who are screening are diagnosed in advanced stages. All of these studies have concluded that annual screening with TVS and CA125 for mutation cancers is ineffective because cancer is not detected at an early enough stage to influence survival. This is why risk-reducing surgery is recommended when child bearing is complete for those with known mutations.[20]

In 2010 and 2011, the US Food and Drug Administration approved the OVA1 test[21] and ROCA with CA125 and HE4.[22] Both tests have the same indications: To be used in women with a pelvic mass to determine the likelihood of malignancy and allow appropriate triage of these women to a gynecologic oncologist. Neither test is approved, or should be used, as a screening test.

DIAGNOSIS

Currently, ACOG recommends that the best way to detect ovarian cancer is for both the patient and her clinician to have a high index of suspicion of the diagnosis in symptomatic women.[4] The Society of Gynecologic Oncologists also recognizes that most women with ovarian cancer are symptomatic, yet go undiagnosed for many months.[2] Unfortunately, no currently available test has been shown to reliably detect ovarian cancer in its earliest and most curable stages, and so educating women and practitioners about symptoms and promptly initiating a diagnostic workup in these women is currently the best method for timely diagnosis.[4]

Historically, ovarian cancer was thought to be a “silent killer” because symptoms were not thought to develop until advanced stages when chances of cure were poor. In the 1980s and 1990s, there were several retrospective studies that evaluated symptoms in ovarian cancer patients.[23–25] All of these studies concluded that women with ovarian cancer frequently have symptoms before diagnosis, although the symptoms were often vague and not necessarily gynecologic in nature. Although

Table 2
Frequency of symptoms in ovarian cancer

Symptom	Frequency (%)
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
None	5

Data from Goff BA, Mandel L, Muntz HG, et al. Ovarian carcinoma diagnosis. Cancer 2000;89: 2068–75.

there was significant agreement across these studies, they were criticized because of small numbers and data collection from retrospective chart analysis.

In 2000, a 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.[26] The findings were significant in that 95% of women with ovarian cancer recalled developing symptoms an average of 3 to 6 months before seeing a physician. The most common symptoms (**Table 2**) were abdominal (77%), gastrointestinal (70%), pain (58%), constitutional (50%), urinary (34%), and pelvic (26%). Ovarian cancer patients often had multiple symptoms; interestingly, gynecologic symptoms were the least common. In women with early stage disease, 89% had symptoms before diagnosis, and symptoms were not different for women with early stage disease compared with those with advanced stages.

This survey also evaluated delays in diagnosis.[26] Physicians and patients both contributed to delays in diagnosis. Physicians commonly misdiagnosed women with irritable bowel syndrome, stress, gastritis, or depression months before the diagnosis of ovarian cancer. In this study, 30% of women were actually treated with a prescription medication for another condition within the 3 to 6 months preceding their ovarian cancer diagnosis. Physician misdiagnosis was associated with more advanced stage of disease. In addition, patients themselves frequently did not recognize their symptoms could be due to a serious diagnosis. Women who said they ignored their symptoms were significantly more likely to be diagnosed with advanced stage disease compared with those who felt they did not ignore their symptoms.

Table 3
Comparison of symptoms between ovarian cancer cases and controls

Symptom	Olson et al,[27] All Stages	Olsen et al,[27] Early Stages	Goff et al,[28] All Stages
Bloating	25.3 (15.5–40.9)	19.2 (9.4–37.5)	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)	5.5 (2.8–10.8)	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)	5.5 (2.5–12.0)	1.6 (0.7–1.4)
Fatigue	2.9 (2.5–6.1)	—	1.4 (0.7–2.7)

Data from Olson SH, Mignone L, Nakraseive C, et al. Symptoms of ovarian cancer. Obstet Gynecol 2001;98:212–7 and Goff BA, Mandel LS, Melancon CH, et al. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. JAMA 2004;291:2705–12.
Values are presented as odds ratios (95% confidence interval).

In 2001, investigators from Memorial Sloan-Kettering Cancer Center published a case-control study evaluating symptoms before diagnosis.[27] Women with ovarian cancer (n = 168) and controls (n = 251) were interviewed about 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. 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 versus late stage disease. When the authors compared symptoms in women with early stage disease with controls assessed by telephone using random-digit dialing (**Table 3**), the odds ratios (OR) were still significant: Bloating (odds ratio [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). Although these results suggested very significant differences between cases and controls, the controls were not women visiting a physician's office, and therefore may not represent the typical patient, with a variety of complaints, seen in clinical practice.

To address the concerns raised about the control group in the Memorial study, researchers at the University of Washington evaluated symptoms typical of ovarian cancer in 1709 women presenting to a primary care clinic. Women were surveyed about the types of symptoms they had experienced over the prior year as well as the frequency, severity, and duration of symptoms.[28] The primary care clinic patients were then compared as controls with a group of 128 women with pelvic masses who filled out an identical survey about symptoms 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, although the OR of symptoms for cases as compared with controls were quite a bit lower than was seen in the Memorial study. One of the potential reasons that the OR are so much lower in the study from Goff and associates is that the control group used were actual patients visiting their primary care physician for a problem visit (see **Table 3**), in contrast with people reached in their home by telephone.

The study from the University of Washington also evaluated the characteristic of symptoms in cancer versus clinic patients.[28] Cancer patients typically reported that

their symptoms occurred 20 to 30 times per month compared with 2 to 3 times per month for the clinic patients. The symptoms in cancer patients were significantly of more recent onset. For instance, the duration of symptoms was usually less than 3 to 6 months for cancer patients compared with a year or longer for the clinic controls. The authors found that 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 the frequency and duration of the symptoms. Researchers from other institutions across the United States and in other countries have found remarkably similar findings.[29–36] In addition, large, population-based studies have identified the majority of ovarian cancer patients as experiencing symptoms before diagnosis.[34,36,37]

A follow-up, case-control study was conducted by Goff and colleagues[38] to establish a symptom index that might be useful in the early diagnosis of ovarian cancer. In this study, 149 women with ovarian cancer were surveyed about symptoms before surgical exploration; controls consisted of 255 women in an ovarian cancer screening program and 233 women who were referred for pelvic ultrasonography. Logistical 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 sensitive for detecting ovarian cancer was a woman having any 1 of 6 symptoms (bloating, increased abdominal size, difficulty eating, feeling full quickly, and abdominal or pelvic pain), which occurred more than 12 times per month and were present for less than 1 year. The overall sensitivity and specificity for detecting ovarian cancer were 70% and 86%, respectively. The sensitivity for detecting early stage disease was 57% and 80% for advanced stage disease. These investigators are currently conducting a clinical trial using symptom triggered screening for ovarian cancer.[39] Women who screen positive on a symptom index (**Fig. 2**) are referred for testing with CA125 and TVS. Critics have raised concerns that evaluation of symptoms will lead to unnecessary operations.[40–43] However, a recent clinical trial of more than 2000 women evaluated with symptom screening followed by symptom-triggered TVS and CA125 found that none of the screened patients underwent a laparotomy or laparoscopy because of enrollment in a symptom screening program.[39] 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, because this is a group for which a screening test neither exists nor is recommended.

One of the main concerns about symptom reporting is the potential of recall bias. However, there have been several case-control studies evaluating symptoms from claims data and chart notes of ovarian cancer patients before their diagnosis.[34,36,37,44] These studies also confirm that women with ovarian cancer are significantly more likely than controls to have specific symptoms 3 to 6 months before diagnosis. Smith and co-workers[37] evaluated the Surveillance, Epidemiology, and End Results Medicare database for 1985 ovarian cancer patients, 6024 breast cancer patients, and 10,941 noncancer patients. ICD-9 diagnosis codes were compared before the ovarian cancer 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 and colleagues[44] performed a chart review of 212 ovarian cancer patients and 1060 controls and found that 85% of cases had 1 of 7 ovarian cancer symptoms documented in the medical records before diagnosis, compared with 15% of controls. Abdominal distension, urinary frequency,

Symptom Index

Are you currently experiencing any of the following symptoms frequently? 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 months you experience each symptom.

1. Pain: Abdominal/Pelvic Pain
   - ❑ No
   - ❑ Yes ⟶ **1a. If yes,** how many **days** per month do you experience this symptom?

     0-5 days ☐ | 6–12 days ☐ | More than 13 days ☐

     1b. If yes, how **long** have you had this symptom?

     Less than 1 month ☐ | 1–6 months ☐ | 7-12 months ☐ | More than 1 year ☐

2. Eating: Feeling full quickly or unable to eat normally
   - ❑ No
   - ❑ Yes ⟶ **2a. If yes,** how many **days** per month do you experience this symptom?

     0-5 days ☐ | 6–12 days ☐ | More than 13 days ☐

     2b. If yes, how **long** have you had this symptom?

     Less than 1 month ☐ | 1–6 months ☐ | 7-12 months ☐ | More than 1 year ☐

3. Abdomen: Abdominal bloating or increased abdomen size
   - ❑ No
   - ❑ Yes ⟶ **3a. If yes,** how many **days** per month do you experience this symptom?

     0-5 days ☐ | 6–12 days ☐ | More than 13 days ☐

     3b. If yes, how **long** have you had this symptom?

     Less than 1 month ☐ | 1–6 months ☐ | 7-12 months ☐ | More than 1 year ☐

Fig. 2. Symptom Index screening tool. (*Adapted from* Goff BA, Lowe KA, Kane JC, et al. Symptom triggered screening for ovarian cancer: a pilot study of feasibility and acceptability. Gynecol Oncol 2012;124:230–5; with permission.)

and abdominal pain were significantly associated with ovarian cancer even at 6 months before diagnosis.

Other investigators have evaluated the University of Washington symptom index retrospectively and have found limited utility.[40,41] In a study by Pavlik and associates,[41] only 6 of 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 and co-workers[40] also retrospectively surveyed women about symptoms before diagnosis and compare this with age-matched controls. In this study, women were surveyed on average of 9

months after diagnosis. 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 PPV and found it to be low, approximately 1%. Because of the low PPV 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 PPV are not surprising given the frequency of these symptoms in the general population and the low incidence of ovarian cancer, but it does not mean that these symptoms should be ignored.

SUMMARY

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. 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 do not have ovarian cancer, it is important that providers include ovarian cancer in their differential diagnosis. Through research from the past decade, we now understand that there are patterns of symptoms associated with ovarian cancer. Importantly, we now know that ovarian cancer is not a "silent disease." Finally, clinicians must always listen carefully to their patients avoid potentially harmful delays in diagnosis. Until there is a screening test, awareness is best.

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