New research shows that symptoms exist in even early-stage ovarian cancer, disproving the myth that it's a "silent killer." Barbara Goff, MD, presents the latest in symptom research, tips on what physicians should be looking for, and what's on the horizon for ovarian cancer screening.

It is well known that when ovarian cancer is detected in early stages cure rates are 70-90% compared to 10-30% for patients who present with advanced stage disease. Even with advanced stage disease there is significant improvement in overall survival (OS) in those patients in whom the surgeon is able to resect all the tumor and leave the patient with no visible residual disease. Recent studies have shown median OS is at least 110 months for those women optimally cytoreduced compared to 36-40 months for those with bulky disease left behind. The factor most predictive of a complete cytoreduction is extent of disease at presentation. Therefore, early detection of ovarian cancer either in Stage I/II or Stage III with minimal tumor bulk has the potential to significantly improve the cure rates for this disease.

Screening for Ovarian Cancer: Challenges and Recent Research
Over the past 20 years there have been significant research efforts directed toward identification of a screening test for ovarian cancer, but unfortunately there continue to be significant challenges that must be overcome before there will be a cost-effective screening test. One of the major barriers to screening is identifying a precursor or in situ lesion. Only recently have researchers identified a potential pre-cancerous lesion for ovarian cancer. Studies of prophylactic salpingo-oophorectomies from BRCA1 and BRCA2 mutation carriers has identified the fallopian tube as the likely site for precursor lesions for most of these patients and possibly most women with high grade serous lesions. One reason "ovarian" cancer screening may not have been successful is that investigators have targeted the wrong organ.

Another major challenge in developing a cost effective test is the low incidence of the disease. In women over 50, the incidence is 40 per 100,000. That means that even with a perfect screening test only 1/2,500 women screened will have ovarian cancer. If the screening test has even a 1% false positive rate then there would be 25 women referred for surgery for each case of cancer detected and would result in a positive predictive value (PPV) of only 4%. In general, the lowest acceptable PPV is 10% or 10 surgeries for each case of cancer detected. In order to have a PPV of 10% a screening test must have a specificity of 99.6% or only a 0.4% false positive rate. In addition, because at least 2,500 women need to be screened to detect a single case of ovarian cancer, the cost must be reasonable, the screening process must be acceptable to women and feasible for providers. Screening tests must successfully detect ovarian cancer in its most curable stages. Finally, we may need different screening strategies for these with family history compared to average-risk women.

Several large clinical trials have been conducted to evaluate the efficacy of ovarian cancer screening. In 2011 the final results of the ovarian portion of The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial were reported. In this study, post-menopausal women were randomized to usual care versus annual CA125 and transvaginal ultrasound for four screens. There were approximately 39,000 women randomized to each arm and they were followed for 13 years. Overall, the PPV of screening tests was under 2%. There was no difference in ovarian cancer mortality between the screened and usual care patients indicating that this screening strategy was ineffective. In addition, of those women who had a false positive screen and underwent surgery, 15% had a significant complication indicating that this screening strategy resulted in harm to women.

The other major trial to evaluate screening, the UK Collaborative Trial Ovarian Cancer Screening
(UKCTOCS)\(^8\) Trial, enrolled over 200,000 post-menopausal women and randomized them to 3 groups: control or usual care, annual TVS or annual CA125 using risk of ovarian cancer followed by TVS (multimodality screening [MMS]). The final results are still not yet reported, but the preliminary results from the prevalence screen were encouraging. In the approximately 50,000 women screened with TVS, 845 (1.8%) underwent surgery; 24 had primary ovarian or fallopian tube cancer, 20 had borderline tumors, and 733 (87%) had benign tumors. Half of the primary ovarian and fallopian tube cancers were diagnosed in early stage. However, because TVS as a primary screen led to many false positives, the PPV of TVS screening was only 5.4%. In the approximately 50,000 women screened with MMS there were only 97 (0.2%) that underwent surgery. Ovarian and fallopian tube cancer was found in 34 women and 47% of those were diagnosed in early stage. Because initial screening with CA125 followed by TVS as a secondary screen led to much fewer false positives, the PPV for MMS was 43.3%. The overall comparison of mortality data from screened women versus controls is still pending and should be reported within the next one-two years. While the PPV for initial screening with CA125 followed by secondary TVS screen (MMS) is encouraging, the screening protocol is quite complex with several to multiple repeat screens required. Feasibility and acceptability outside of a clinical trial must be determined as well as the cost effectiveness of such a program.

Current recommendations by the American Congress of Obstetricians and Gynecologists (ACOG)\(^9\) and the Society of Gynecologic Oncology (SGO)\(^10\) are that screening should not be offered to average-risk women. The US Preventive Services Task Force (USPSTF) gives ovarian cancer screening a “Grade D” recommendation, which means there is fair evidence to recommend its exclusion at the time of a periodic health exam because women are more often harmed from screening because of false positives.\(^11\) The USPSTF gives genetic testing/counseling in men and women with a family history of cancer a “Grade B” recommendation because there is fair evidence for significant benefit.\(^12\) Screening for ovarian cancer in women with a family history or genetic testing that indicate they are at elevated risk is not discouraged. However, studies have not shown that screening actually reduces the morbidity or mortality of ovarian cancer in these patients.\(^13-16\) This is why risk reducing surgery should be discussed and considered for all of these high-risk women.

Symptoms of Ovarian Cancer: Why it Can No Longer be Considered a "Silent Killer"

Currently the diagnosis of ovarian cancer is made when a clinician has a high index of suspicion in a symptomatic patient.\(^9\) Both the SGO and ACOG recommend that the education of women and practitioners about symptoms and a prompt diagnostic workup is currently the best method to make a diagnosis.\(^9,10\) Historically ovarian cancer was considered a “silent killer” because symptoms weren’t supposed to develop until the disease was too far advanced to make a difference.\(^3\) However, over the last decade there has been a large amount of research showing that women with ovarian cancer do, in fact, present with symptoms, even in early stages.\(^17-25\)

The first large study to evaluate symptoms in women with ovarian cancer was published in 2000.\(^17\) In this study 1,725 women were surveyed about symptoms prior to diagnosis and potential delays in diagnosis. In this study, 95% of women had symptoms preceding their diagnosis and 89% of women with early stage disease experienced symptoms an average of 3-6 months prior to diagnosis. Symptoms typical of ovarian cancer are abdominal and pelvic pain, bloating, feeling full quickly, difficulty eating and urinary symptoms. Ovarian cancer patients often had multiple symptoms and interestingly, gynecologic symptoms are the least common and gastrointestinal symptoms are the most. This survey also evaluated delays in diagnosis.\(^17\) 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.

Additional case control series using patient reported symptoms without recall bias, including review of chart notes and billing diagnosis codes prior to patients knowing if they had cancer or not also confirm that ovarian cancer patients are significantly more likely to have symptoms that are GI,
abdominal, pelvic, and urinary prior to their diagnosis. While these are symptoms common to many disease, what seems to distinguish these symptoms as being predictive of ovarian cancer include that the symptoms have persisted for more than three weeks and they occur almost daily. In addition, women will often have multiple symptoms at the time of diagnosis.

Based on a case control study, a symptom index (SI) for ovarian cancer detection was developed. The SI which is most sensitive for detecting ovarian cancer is having 1 of 6 symptoms (bloating, increased abdominal size, difficulty eating, feel full quickly, and abdominal or pelvic pain), which occur 13 times per month and are present for less than 1 year. (Figure 1) The overall sensitivity and specificity for detecting ovarian cancer with the SI are 70% and 86%, respectively. The sensitivity for detecting early stage disease was 57% and 80% for advanced stage disease.

Recently, there have been several reports of symptom triggered screening for ovarian cancer. Goff, et al conducted a pilot study to assess feasibility and acceptability of symptom triggered screening in a primary care clinic. Using the SI as a primary screen in women age 40 and older, 2,261 women participated. If the SI was positive then additional testing with CA125 and TVS was performed. In addition, patients and providers were surveyed as to their satisfaction with the screening process. Overall, both patients and providers found the screening process acceptable and added only negligible time to the visit. A total of 4% of primary care patients were SI positive and went on to receive additional screening with CA125 and TVS. Of these patients, one was diagnosed with ovarian cancer. There was one SI negative patient diagnosis with ovarian cancer. This screening process resulted in minimal additional procedures (two endometrial biopsies and one hysteroscopy). While this pilot study was too small to assess sensitivity and specificity, it did confirm that symptom triggered screening was feasible, acceptable and safe, resulting in minimal study related procedures. These investigators have continued to enroll patients in this screening protocol to assess cancer outcomes.

In a similar study, Gilbert et al recruited women age 50 and older with symptoms typically associated with ovarian cancer to participate in a study. Recruitment was done by direct marketing to the public. Women with suspicious symptoms were offered CA125 and TVS. In their study they found that 1 out of every 132 symptomatic women was diagnosed with ovarian cancer as compared to 1/3000 in their general population. Early stage ovarian cancer was found in 36%, small volume Stage III disease in 36%, and advanced stage suboptimal in 27% of the study population. When they compared ovarian cancer patients in the general clinic population of Montreal, where the study was conducted, to the study patients they found that only 44% of these patients were diagnosed in early or small volume Stage III disease and 56% were advanced stage suboptimal. This suggests that identification of ovarian cancer patients through symptoms may allow for earlier diagnosis, but results must be confirmed.

Both the Goff, et al and Gilbert, et al studies show that it is possible to screen for ovarian cancer with a symptom triggered approach. 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.

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 patient and her provider. 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 13 times per month and are of recent onset, then ovarian cancer should be considered as a possible diagnosis. 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 know that ovarian cancer is not a “silent disease.” Finally, clinicians must always listen carefully to their patients to avoid potentially harmful delays in diagnosis. Until there is a screening test, awareness is best.

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