



# Screening for Ovarian Cancer in Midlife Women

Emma Rossi, MD; Daniel L. Clarke-Pearson, MD

**Diagnosis of ovarian cancer is challenging, and routine screening is not recommended. However, women with a defined genetic predisposition may benefit from regular screening and evaluation.**

Ovarian cancer accounts for only 3% of female cancers but is the fifth leading cause of all cancer-related deaths in American women. A total of 15,520 women died from ovarian cancer in the United States in 2008.<sup>1</sup> Nearly two-thirds are diagnosed at an advanced stage (III and IV), with a 5-year survival of approximately 33%. In contrast, the 5-year survival of women with cancers confined to the ovary is approximately 90%. This disparity motivates research into screening for early-stage ovarian cancer. An effective screening tool that reduces the mortality from ovarian cancer remains elusive.

## Screening Tests For Ovarian Cancer

The concepts of predictive value, sensitivity, and specificity are critical in determining the usefulness of screening tests. “Sensitivity” is the term used to describe the proportion of patients with ovarian cancer who will have a positive test, and “specificity” is a measurement of the proportion of patients without ovarian cancer who return a negative test result. The positive predictive value (PPV) of a test reflects the probability that a patient who has a positive test result truly has ovarian cancer.

The strength of a test’s PPV is directly related to the prevalence of the disease in the screened population. Therefore, given the relatively low prevalence of ovarian

cancer in the general population, it is difficult for even a very sensitive or specific tool to return an acceptable PPV. Most epidemiologists regard 10% as the minimum PPV to support a screening test.<sup>2</sup>

## ◀ FOCUSPOINT

*One woman in 10 with a positive screening test will have ovarian cancer, while the remaining 9 will be exposed to surgical risks, costs, and recovery in the absence of the disease.*

With these parameters, one woman out of 10 with a positive test will have ovarian cancer, while the remaining 9 will be exposed to surgical risks, costs, and recovery in the absence of ovarian cancer.

## Ultrasonography

Transvaginal ultrasound is used to evaluate the size and structure of a woman’s

---

**Emma Rossi, MD**, is a clinical fellow in Gynecologic Oncology, Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill.

**Daniel L. Clarke-Pearson, MD**, is Chair, Department of Obstetrics and Gynecology, and Robert A. Ross Professor, University of North Carolina at Chapel Hill School of Medicine.

ovaries. Healthy asymptomatic women have a defined normal upper limit of ovarian volume.<sup>3</sup> Architectural features that can be used to discriminate benign from malignant ovarian neoplasm include cyst wall septations greater than 3 mm and cyst papillations or solid components.<sup>4</sup> When ovarian morphology indices using ovarian size and architecture features have been retrospectively applied, their reported sensitivity is between 89% and 100%, with a specificity ranging between 70% and 83%.<sup>4,5</sup> These values come from symptomatic populations with increased baseline prevalence and achieve higher PPVs than would be expected in the general

estimation of ovarian cancer risk.<sup>12</sup> When 33,621 CA-125 samples from 9,233 women were retrospectively assessed, an increasing trend in CA-125 was associated with a sensitivity of 86% for the preclinical detection of ovarian cancer (as compared with 62% sensitivity when only a single value of CA-125 was considered).<sup>13</sup> This measure, called the risk of ovarian cancer (ROC), was confirmed to have a high PPV (19%) in a subsequent prospective study of postmenopausal women.<sup>14</sup>

### Alternative Tumor Markers

Other tumor markers have been analyzed in combination with CA-125 with the goal of improving sensitivity, specificity, and PPV. The interpretation of tumor marker panels relies on the pattern of their levels in relationship to each other, rather than the absolute levels of each marker. Over 30 different serum tumor markers have been evaluated in combination with CA-125.<sup>15</sup> In general, sensitivity has been increased by 5% to 10%, but with an associated decline in specificity.

OVA1™ is a serum test that evaluates 5 biomarkers (transthyretin, apolipoprotein A-1, β2 microglobulin, transferrin, and CA-125 II) in women with an ultrasound-confirmed adnexal mass who are intended for surgery, with results indicating the probability of malignancy.<sup>16</sup> This test is FDA approved for use only in combination with positive imaging (such as ultrasound) and clinical evaluation to determine the need for preoperative subspecialist referral.

Human epididymis specific protein 4 (HE4) is a müllerian-derived glycoprotein whose secretion is highly restricted in normal tissues.<sup>17</sup> It is FDA approved for use in surveillance of recurrence or progression in women with an established diagnosis of epithelial ovarian cancer. *Neither of these tests are recommended or approved for use in the screening of asymptomatic women.*

### Symptoms Survey

In a national ovarian cancer survey, approximately 95% of women with ovarian

### FOCUSPOINT ►

*Routine screening of the general, average-risk population for ovarian cancer is not recommended.*

population. When average-risk women were screened with ultrasound, ovarian cancer was confirmed in 1.3% to 8% of women with a positive test.<sup>6-8</sup>

### Cancer Antigen-125

Serum tumor markers are attractive tools for ovarian cancer screening because they are widely available, noninvasive, and objective. Cancer antigen (CA)-125 is a serum protein elevated in approximately 80% of women with advanced-stage ovarian cancer but only 1% to 2% of the normal population.<sup>9</sup> Unfortunately, this protein is within normal range for more than half of women with stage I ovarian cancer.<sup>10</sup> The specificity for this test is poor, because a number of benign conditions may result in elevated CA-125 levels.

CA-125 has superior specificity in postmenopausal women compared with premenopausal women (98.5% and 94.5%, respectively).<sup>11</sup> The examination of CA-125 values over time improves the

cancer reported that they had symptoms preceding their diagnosis (particularly abdominal pain, bloating, early satiety, and bladder or bowel dysfunction).<sup>18</sup> A symptom index has been created that incorporates these commonly reported experiences.<sup>19</sup> This index has also been described in combination with CA-125 measurement and transvaginal ultrasonography.<sup>20,21</sup>

These studies failed to show an improvement in specificity or accuracy for the combined approach, possibly because it was studied in high-risk women (who may be more likely to overreport symptoms) or, in the case of ultrasound, applied retrospectively to those with confirmed ovarian cancer, in which case ultrasound alone proved to be most accurate. There are ongoing studies to prospectively evaluate the role of the symptom index when applied for screening in average-risk populations.

### Combined Modality Screening and RCTs

Ultrasonography, measurement of tumor markers, and patient-reported symptom indices in isolation have not demonstrated the sensitivity, specificity, and PPV necessary to justify screening for ovarian cancer in average-risk populations of postmenopausal women. The use of combined modality screening (age-stratified CA-125 levels and subsequent transvaginal ultrasound) has been named the ROC algorithm. The use of this algorithm in a prospective, multicenter screening study of 3,238 postmenopausal, average-risk women progressed only 8 women to surgery and showed good positive predictive value (37.5%), with 3 early-stage invasive cancers found.<sup>22</sup> Long-term survival data from this group of women are not yet available.

Large prospective randomized controlled trials (RCTs) in both the United States and United Kingdom are reviewing combined modality assessment for screening. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

is a US-based RCT that has enrolled 34,261 healthy, average-risk women ages 55 to 74 to receive either annual CA-125 testing plus transvaginal ultrasonography or “usual care.”<sup>27</sup> The study is now in follow-up phase. Ovarian cancer was found in 5% of women undergoing surgery following a positive test result, with the majority of the cancers found in advanced stages. The PPV of this combination testing in the average-risk population was 1.3%. Long-term follow-up is not yet complete, and final results are anticipated in 2014.

The UK Collaborative Trial of Ovarian Cancer Screening is following 202,638 average-risk, postmenopausal women who were randomized to no treatment, multimodality screening (ultrasound and CA-125), or yearly ultrasound screening.<sup>23</sup> At 3 years follow-up, multimodality screening was associated with a 35.1% PPV, compared to 2.8% for ultrasound screening alone. Of the invasive cancers identified, 48.3% were stage I/II. The increased detection of ovarian cancer in this study has yet to be associated with improved overall survival.

### Guidelines

Routine screening of the general, average-risk population for ovarian cancer is not recommended by any professional society.<sup>24,25</sup>

### Conclusion

Ovarian cancer is a serious disease made more challenging by our limited ability to achieve diagnosis at an early, curable stage. Routine screening of average-risk, postmenopausal women with current technologies is not recommended at this time. However, women who have a defined genetic predisposition to ovarian cancer may benefit from regular screening ultrasonography and CA-125 evaluations. We await the overall survival data from large RCTs of screening average-risk women and data from evolving research into new serum markers. Clinicians and patients should pay close attention to symptoms

and family history, reserving testing for diagnostic rather than screening purposes.

*The authors report no actual or potential conflicts of interest in relation to this article.*

### References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin.* 2008;58(2):71-96.
2. Clarke-Pearson DL. Clinical practice. Screening for ovarian cancer. *N Engl J Med.* 2009;361(2):170-177.
3. Pavlik EJ, DePriest PD, Gallion HH, et al. Ovarian volume related to age. *Gynecol Oncol.* 2000;77(3):410-412.
4. DePriest PD, Varner E, Powell J, et al. The efficacy of a sonographic morphology index in identifying ovarian cancer: a multi-institutional investigation. *Gynecol Oncol.* 1994;55(2):174-178.
5. Sassone AM, Timor-Tritsch IE, Artner A, Westhoff C, Warren WB. Transvaginal sonographic characterization of ovarian disease: evaluation of a new scoring system to predict ovarian malignancy. *Obstet Gynecol.* 1991;78(1):70-76.
6. Sato S, Yokoyama Y, Sakamoto T, Futagami M, Saito Y. Usefulness of mass screening for ovarian carcinoma using transvaginal ultrasonography. *Cancer.* 2000;89(3):582-588.
7. Partridge E, Kreimer AR, Greenlee RT, et al. Results from four rounds of ovarian cancer screening in a randomized trial. *Obstet Gynecol.* 2009;113(4):775-782.
8. Hayashi H, Yaginuma Y, Kitamura S, et al. Bilateral oophorectomy in asymptomatic women over 50 years old selected by ovarian cancer screening. *Gynecol Obstet Invest.* 1999;47(1):58-64.
9. Bast RC Jr, Klug TL, St John E, et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. *N Engl J Med.* 1983;309(15):883-887.
10. Woolas RP, Xu FJ, Jacobs IJ, et al. Elevation of multiple serum markers in patients with stage I ovarian cancer. *J Natl Cancer Inst.* 1993;85(21):1748-1751.
11. Einhorn N, Sjøvall K, Knapp RC, et al. Prospective evaluation of serum CA 125 levels for early detection of ovarian cancer. *Obstet Gynecol.* 1992;80(1):14-18.
12. Skates SJ, Xu FJ, Yu YH, et al. Toward an optimal algorithm for ovarian cancer screening with longitudinal tumor markers. *Cancer.* 1995;76(10 Suppl):2004-2010.
13. Skates SJ, Menon U, MacDonald N, et al. Calculation of the risk of ovarian cancer from serial CA-125 values for premenopausal women. *J Clin Oncol.* 2003;21(10 Suppl):206s-210s.
14. Menon U, Skates SJ, Lewis S, et al. Prospective study using the risk of ovarian cancer algorithm to screen for ovarian cancer. *J Clin Oncol.* 2005;23(31):7919-7926.
15. Bast RC Jr, Badgwell D, Lu Z, et al. New tumor markers: CA125 and beyond. *Int J Gynecol Cancer.* 2005;15(Suppl 3):274-281.
16. OVA1™ Test [package insert]. Freemont, CA: Vermillion; 2009.
17. Drapkin R, von Horsten HH, Lin Y, et al. Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas. *Cancer Res.* 2005;165(6):2162-2169.
18. Goff BA, Mandel L, Muntz HG, Melancon CH. Ovarian carcinoma diagnosis. *Cancer.* 2000;89(10):2068-2075.
19. Goff BA, Mandel LS, Drescher CW, et al. Development of an ovarian cancer symptom index: possibilities for earlier detection. *Cancer.* 2007;109(2):221-227.
20. Andersen MR, Goff BA, Lowe KA, et al. Combining a symptoms index with CA 125 to improve detection of ovarian cancer. *Cancer.* 2008;113(3):484-489.
21. Pavlik EJ, Saunders BA, Doran S, et al. The search for meaning—Symptoms and transvaginal sonography screening for ovarian cancer: predicting malignancy. *Cancer.* 2009;115(16):3689-3698.
22. Lu KH, Skates S, Bevers TB, et al. A prospective US ovarian cancer screening study using the risk of ovarian cancer algorithm (ROCA). *J Clin Oncol.* 2010;28:7s (suppl, abstr 5003).
23. 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(4):327-340.
24. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: ovarian cancer and genetic screening. Available at: [www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Accessed May 26, 2011.
25. ACOG Committee on Gynecologic Practice. The role of the generalist obstetrician-gynecologist in the early detection of ovarian cancer. *Gynecol Oncol.* 2002;87(3):237-239.

### Audio Cast Breaking News Alert

#### The Impact of Sexual Symptoms on Women in Menopause

Listen to Dr Michael Krychman discuss the latest results from the HealthyWomen's survey.



To access the online audio cast, scan the barcode or go to the multimedia tab at [www.femalepatient.com](http://www.femalepatient.com).



For a **PATIENT HANDOUT** on ovarian cancer in midlife women, see page 49.