

## LEARNING OBJECTIVES

- Describe the reasons why ovarian cancer is difficult to detect early in the course of the disease
- Discuss the role of risk factors for ovarian cancer, especially genetics
- Review the types of ovarian cancer and their unique features
- Explain two important screening tools—biomarker CA-125 and transvaginal ultrasound

# Ovarian cancer: The search for an accurate screening technique

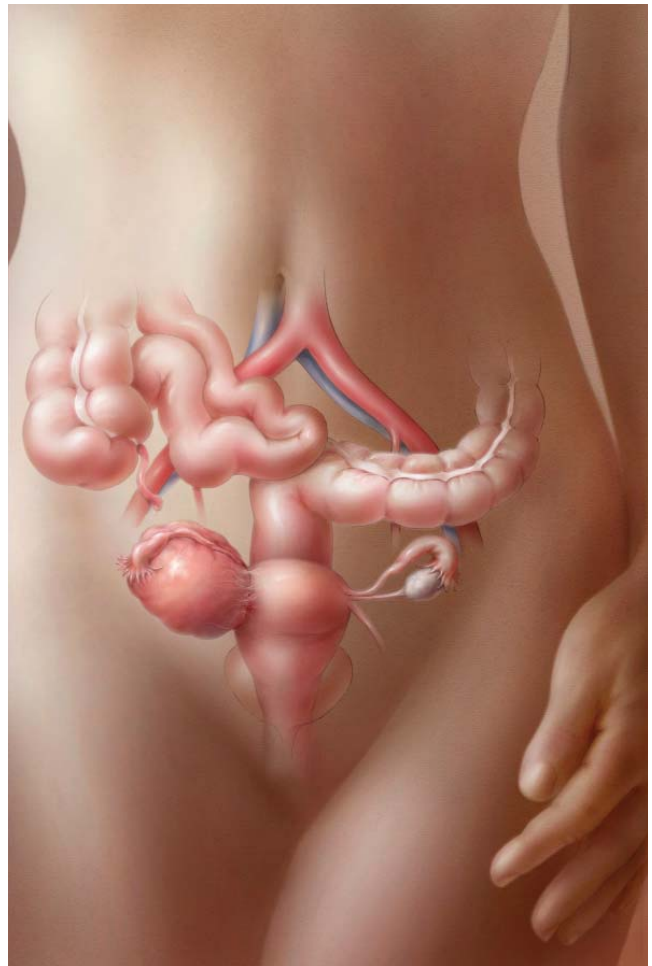
Few cases of ovarian cancer are diagnosed in the early stage; however, new modalities promise earlier detection and a better prognosis for patients.

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Ovarian cancer is known to be an extremely aggressive and deadly disease that affects women worldwide. The disease accounts for 14,300 deaths in the United States each year and is ranked fourth in cancer deaths among women.<sup>1</sup> The prevalence in the general population remains low at 1% to 2%;<sup>2</sup> however, the mortality rate exceeds that of all other gynecologic malignancies combined.<sup>1</sup> Estimates show that ovarian cancer can shorten a woman's life by an average of 18 years.<sup>3</sup> The low survival rate is largely attributed to the fact that most cases are not diagnosed until the disease has progressed to an advanced stage.<sup>4</sup> Only 20% of tumors are found in stage I, which has a promising 90% to 95% 5-year survival rate.<sup>5</sup> Most tumors are found at later stages, which results in an overall cure rate of only 45%.<sup>1</sup>

## CHALLENGES TO EARLY DETECTION

Ovarian cancer is difficult to detect early in the course of the disease for several reasons. The main factor is that ovarian cancer has no specific signs or symptoms. Typically, patients experience very vague symptoms, many of which are not considered to indicate cancer of the ovaries.<sup>1</sup> A recent retrospective analysis reported that 95% of women with ovarian cancer experienced symptoms; however, not all were gynecologic in nature.<sup>6</sup> Early symptoms may be abdominal discomfort; early satiety; changes in bowel habits, such as diarrhea or constipation; frequent urination; and dull back pain.<sup>3,7</sup> Late symptoms include anorexia, nausea, vomiting, increased abdominal girth, ascites, weight gain, and chronic pelvic or abdominal pain.<sup>3</sup> Some patients are completely asymptomatic. Therefore, the disease progresses silently and is not found until it has metastasized to other organ systems. A study of 1,700 women with



Location of the ovaries makes early detection difficult.

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ovarian cancer found that 5% of the women reported no symptoms prior to diagnosis; on the other hand, more than 70% of the women reported having symptoms for 3 months or longer.<sup>7</sup> The low incidence of the disease is another reason why many cases of ovarian cancer continue to be missed.

Female anatomy poses a challenge as well. The ovaries lie deep in the pelvic viscera, which makes palpation during physical examination difficult.<sup>3</sup> As a result, small, early tumors are usually not palpable.<sup>5</sup> Ovarian size in postmenopausal women, women weighing more than 200 lb, or women with an enlarged uterus is difficult to assess in a pelvic examination.<sup>8</sup> Furthermore, unlike the cervix, vagina, or vulva, direct visualization or biopsy of the ovaries cannot be obtained without an invasive procedure.<sup>3</sup>

Early detection is clearly the key to abolishing ovarian cancer, and screening modalities are necessary to accomplish this. However, reliable screening techniques have been tremendously difficult to develop. No recommendations suggest that screening would be beneficial for the general population or even for just a subset of women considered to be at high risk. Typically, in the clinical setting, women are screened when they have a strong family history of ovarian cancer or a known breast cancer gene mutation. The hope is that we will have a reliable and cost-effective method that will enable us to screen all women, not just those considered to be at high risk.

Researchers continue to study the different types and distinctive qualities of ovarian cancer. The roles of risk factors and symptoms are being studied and can lead to the development of a reliable screening modality. Serial cancer antigen 125 (CA-125) measurements and transvaginal sonography (TVS) are the most commonly used screening techniques. However, both techniques have limitations, and researchers continue to look for ways to detect ovarian malignancies earlier in the disease process in the hope of increasing the chance for survival.

### THE ROLE OF RISK FACTORS

The lifetime risk of developing ovarian cancer is low; however, certain factors can increase that risk by 11% to 65%.<sup>3</sup> Genetics,

hormones, reproduction, and lifestyle choices all play a role.<sup>7</sup> Genetics is the most significant risk factor. A woman with one family member who received a diagnosis of ovarian cancer has a 4% to 5% risk of developing the disease herself; this increases to 7% if two or more family members have been affected.<sup>7</sup> In addition, carriers of the *BRCA1* or *BRCA2* gene mutation are at even greater risk. For a woman with the *BRCA1* gene mutation, the risk of developing ovarian cancer is 20% to 40% and the cancer usually manifests in the late 40s.<sup>9,10</sup> For a woman with the *BRCA2* mutation, the risk is 10% to 20% and the cancer typically manifests during the sixth decade.<sup>9,10</sup> A woman with either mutation has a 6- to 60-fold increased chance of developing ovarian cancer by age 70 years compared to the general population.<sup>10</sup> Although screening may benefit these women, screening frequency has not been agreed upon. These patients are sometimes told to consider a prophylactic bilateral salpingo-oophorectomy (PBSO).<sup>9</sup> In fact, the researchers in one study determined that PBSO should be the only way to manage high-risk patients.<sup>2</sup>

Ovarian cancer risk also increases with age. The median age at diagnosis is 63 years. The incidence of ovarian cancer increases until age 80 years and then begins to decline.<sup>7</sup> Hormonal factors and reproductive history appear to affect overall risk as well. Nullparity, infertility, early menarche, and late menopause are factors that increase the risk of disease. However, using an oral contraceptive for as little as 3 to 6 months may lower the risk of developing ovarian cancer by as much as 30% to 60%.<sup>7</sup> Pregnancy, breast-feeding, tubal ligation, and PBSO are also considered to be protective against ovarian cancer.<sup>7</sup>

Lifestyle factors such as physical activity, diet, and frequency of routine medical visits may also affect ovarian cancer risk. One study's findings suggested that physical activity decreases estrogen exposure, reduces ovulation frequency, and, consequently, decreases progesterone exposure during the luteal phase of the menstrual cycle.<sup>11</sup> The researchers believe that lower hormone exposure decreases the risk of ovarian cancer.<sup>11</sup> The relationship of diet to cancer risk was also included in the study. Diets rich in vegetables and fish

### KEY POINTS

- The prevalence of ovarian cancer in the general population remains low at 1% to 2%; however, the mortality rate exceeds that of all other gynecologic malignancies combined. Estimates show that ovarian cancer can shorten a woman's life by an average of 18 years. The low survival rate is largely attributed to the fact that most cases are not diagnosed until the disease has progressed to an advanced stage.
- Ovarian cancer is difficult to detect early in the course of the disease for several reasons. The main factor is that ovarian cancer has no specific signs or symptoms. Typically, patients experience very vague symptoms, many of which are not considered to indicate cancer of the ovaries.
- Genetics is the most significant risk factor. A woman with one family member who received a diagnosis of ovarian cancer has a 4% to 5% risk of developing the disease herself; this increases to 7% if two or more family members have been affected. In addition, carriers of the *BRCA1* or *BRCA2* gene mutation are at even greater risk.
- The cost of establishing a nationwide ovarian cancer screening program for women aged 45 years and older is estimated to be \$14 billion. The high cost of screening, coupled with the low prevalence of ovarian cancer, hinders implementation of a screening program for the general population.
- Health care providers should maintain a high level of suspicion for ovarian cancer even though prevalence is low. Although the signs and symptoms are vague and nonspecific, clinicians need to be attuned to their patients' symptoms. Ovarian cancer should be in the differential if a patient presents with vague, nonspecific symptoms.

were found to reduce the risk, whereas diets high in meats and fats were found to increase risk.<sup>11</sup>

Another study found a correlation between ovarian cancer and regular medical check-ups. This study's findings indicated a higher incidence of ovarian cancer among women who did not have regular medical check-ups, pelvic examinations, or an established primary care provider. This association was found to be even more significant in postmenopausal women.<sup>12</sup>

### TYPES OF OVARIAN CANCER

Ovarian cancer is classified into several types and each has unique features. The three major pathologic ovarian cancers are germ cell, sex-cord stromal, and epithelial. The most common type is epithelial.

**Germ cell tumors** develop from precursors of the ova. The most common malignancy of this type is the dysgerminoma.<sup>7</sup>

**Sex-cord stromal** cells most often cause granulose-cell tumors by secreting hormones and connecting different parts of the ovary.<sup>7</sup> **Epithelial ovarian cancer** is the most frequently occurring form, accounting for more than 90% of the cases.<sup>7</sup> This type arises from the germinal epithelium or mesothelium of the ovary. The subtypes of epithelial ovarian cancer are serous, mucinous, endometrioid, and clear cell.

**Serous epithelial tumors** make up 70% of all epithelial ovarian cancers.<sup>13</sup> This tumor typically develops in both ovaries and is usually not diagnosed until the disease has progressed to stage III or IV. Serous epithelial ovarian cancer is defined as *low grade* or *high grade*. Low-grade tumors tend to be detected more easily during screening. Conversely, high-grade tumors often go undetected and they also metastasize early. Unfortunately, most serous epithelial tumors are high-grade tumors.

**Mucinous epithelial tumors** account for 5% to 10% of all epithelial cancers. They tend to affect only one ovary and are often low-grade malignancies. They are commonly stage I tumors at diagnosis.<sup>13</sup>

**Endometrioid tumors** account for 20% of epithelial ovarian cancers. Endometrioid tumors are usually associated with endometriosis. Fifteen percent to 20% of patients with this type of tumor also have endometrial cancer.<sup>13</sup>

**Clear cell tumors** account for 5% to 10% of epithelial ovarian cancer cases. They are also associated with endometriosis. These tumors are usually confined to the ovary at the time of diagnosis.<sup>13</sup>

### PROMISES AND PITFALLS OF SCREENING

The ideal screening modality would enable clinicians to detect ovarian cancer at the earliest stage of disease, thereby increasing the rate of survivability in the screened population;<sup>4</sup> in addition, it would be cost-effective. The cost of establishing a nationwide ovarian cancer screening program for women aged 45 years and older is estimated to be \$14 billion.<sup>14</sup> The high cost of screening, coupled with the low prevalence of ovarian cancer, hinders implementation of a screening program for the general population.

Accuracy is another factor to take into account. A positive screen may lead to an invasive procedure; therefore, the

screening modality must have a high sensitivity and specificity. Most gynecologic surgeons agree that an appropriate positive predictive value (PPV) would be 10%.<sup>15</sup> In other words, at least one ovarian cancer diagnosis needs to be made for every 10 surgical interventions based on a positive screen. A PPV of 10% would be achieved with a sensitivity of at least 75% and specificity of at least 99.6%.<sup>15</sup>

Researchers working to develop an effective screen for ovarian cancer have focused on CA-125 measurements and TVS. However, neither of these modalities has a PPV of 10%. New trials of these modalities and alternatives are ongoing.

**Biomarkers** CA-125 is the most promising of the biomarkers under investigation as a potential screen for early detection of ovarian cancer.<sup>16</sup> CA-125 is a protein antigen normally found in the blood serum. In healthy women, the CA-125 level is below 35 U/ $\mu$ L.<sup>5</sup> The level tends to be higher in women with later stages of ovarian cancer. Two studies found a higher CA-125 level in 82% and 85% of women

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with stage III and IV ovarian cancers, respectively.<sup>3,5</sup> Unfortunately, early-stage ovarian cancers are not necessarily identifiable by an elevated CA-125 level. Only 50% of women with stage I ovarian cancer had a CA-125 level above 35 U/ $\mu$ L.<sup>17</sup> Furthermore, CA-125 is not specific for ovarian malignancies, especially in premenopausal women. Elevated CA-125 levels can also be the result of nonmalignant conditions such as endometriosis, menstruation, pregnancy, and presence of ovarian cysts. The sensitivity is 50% to 60% and specificity is 78%; therefore, CA-125 measurement would not be an effective ovarian cancer screening tool for the general population.<sup>5</sup> The risk of false-positive and false-negative results is too high. On the other hand, CA-125 is a very helpful tool for monitoring ovarian cancer progression. CA-125 levels have been noted to decline in response to therapy, whereas levels increase as the cancer progresses.<sup>1</sup>

Researchers are striving to find a way to make CA-125 measurement a useful and accurate screening tool. Increasingly, the focus of studies is on using a panel of several specific biomarkers. One study used three biomarkers: CA-125, OVX1, and macrophage colony-stimulating factor. Investigators found that 98% of patients with stage I ovarian cancer had an elevated level of at least one of these biomarkers. Although increasing the number of biomarkers that are measured would improve sensitivity, it would decrease specificity.<sup>5</sup> However, biomarker panels are expected to be used successfully for ovarian cancer screening within the next 5 to 10 years.<sup>5</sup>

**Transvaginal sonography** TVS is commonly used for ovarian cancer screening. Data analysis shows that the use of TVS is safe and most patients tolerate the procedure very well. No complications are associated with TVS and fewer than 10 of 100,000 women complained that the procedure was uncomfortable. TVS is time efficient (a complete screen can be performed in only 5 to 10 minutes) and is cost efficient in facilities where it is commonly used.<sup>4</sup> Although there are many positives, TVS does have some limitations. TVS can identify abnormal ovarian morphology or volume but cannot accurately distinguish between benign and malignant tumors.<sup>18</sup> In a study involving 15,000 asymptomatic women, the sensitivity and specificity of TVS for identifying ovarian tumors was 81% and 98%, respectively. However, TVS could not reliably differentiate the malignant lesions from the benign ones. Consequently, 180 women underwent surgical procedures but only 17 had ovarian cancer, a PPV of only 9.4%. In addition, four women developed ovarian cancer 12 months after a negative screening result.<sup>3</sup> Two other studies also showed poor results when using TVS to detect early-stage ovarian cancer in high-risk women. Sensitivity was only 25% in one study and 31% in the other study.<sup>16</sup>

**Multimodal screening** The discouraging results of CA-125 or TVS alone have encouraged researchers to try multimodal screening: CA-125 in conjunction with TVS. A large, randomized study involving 22,000 women was conducted in the United Kingdom to test the effects of multimodal screening. The women were divided into a control group and a screened group. CA-125 levels were measured three times per year in the screened group. Of these women, 468 were found to have elevated CA-125 levels; consequently, TVS was performed. Twenty-nine women underwent surgery after TVS results showed an abnormality. Ovarian cancer was detected in 6 of these women, yielding a PPV of 20.7%. This study clearly demonstrated that TVS has an extensive capability of detecting ovarian abnormalities but a limited ability to determine which abnormality is likely to be a malignancy.<sup>3</sup> Still, the results showed that the combination of CA-125 and TVS provided the best results. A current study is recruiting up to 200,000 postmenopausal women. These women are being assigned to one of three groups: a control group, an ultrasound group, or a multimodal screening group. In addition to determining the benefits of multimodal screening, this study will examine the relative issues concerning health economics, adherence to screening, potential target populations, screening-related stress, and physical morbidity.<sup>3</sup>

**Proteomics** This new approach has created some excitement. Proteomics is an area of genetics that examines the full set of proteins encoded by a genome. Researchers are applying this concept to ovarian cancer by comparing the proteins in the serum of women with ovarian cancer to the proteins of women who do not have ovarian cancer. The researchers identified five protein peaks present in women with ovarian cancer but not in those who are disease-free. Researchers are hopeful that proteomics can be used to accurately identify stage I ovarian cancers in the near future.<sup>3</sup>

## CONCLUSION

Efforts to identify a safe, cost-effective, and accurate screen for ovarian cancer are ongoing. Presently, the shortcomings of the current screening modalities and the need for invasive follow-up procedures for a definitive diagnosis inhibit making formal recommendations. In the meantime, health care providers should maintain a high level of suspicion for ovarian cancer even though prevalence is low. Although the signs and symptoms are vague and nonspecific, clinicians need to be attuned to their patients' symptoms. Ovarian cancer should be in the differential if a patient presents with vague, nonspecific symptoms. High-risk patients should be considered for screening, but clinicians must maintain a cautious awareness of the possibility of false-positive and false-negative results.

Furthermore, patient education cannot be stressed enough. A vital role of the health care provider is to emphasize the importance of routine examinations and follow-up care. In addition, the patient should be made aware of the importance of relaying accurate personal and family history. With these efforts combined, clinicians can strive to make it more likely that ovarian cancer will be found at an early stage and will be less likely to go undetected. **JAAPA**

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## REFERENCES

1. Mani R, Jamil K, Vamsy MC. Specificity of serum tumor markers (CA125, CEA, AFP, Beta HCG) in ovarian malignancies. *Trends Med Res*. 2007;2(3):128-134.
2. Woodward ER, Sleightholme HV, Considine AM, et al. Annual surveillance by CA125 and transvaginal ultrasound for ovarian cancer in both high-risk and population risk women is ineffective. *BJOG*. 2007;114(12):1500-1509.
3. Fields MM, Chevlen E. Ovarian cancer screening: a look at the evidence. *Clin J Oncol Nurs*. 2006;10(1):77-81.
4. van Nagell JR Jr, DePriest PD, Ueland FR, et al. Ovarian cancer screening with annual transvaginal sonography: findings of 25,000 women screened. *Cancer*. 2007;109(9):1887-1895.
5. Yurkovetsky ZR, Linkov FY, E Malehorn D, Lokshin AE. Multiple biomarker panels for early detection of ovarian cancer. *Future Oncol*. 2006;2(6):733-741.
6. Rufford BD, Jacobs LJ, Menon U. Feasibility of screening for ovarian cancer using symptoms as selection criteria. *BJOG*. 2007;114(1):59-64.
7. Martin VR. Ovarian cancer: an overview of treatment options. *Clin J Oncol Nurs*. 2007;11(2):201-207.
8. van Nagell JR, DePriest PD. Management of adnexal masses in postmenopausal women. *Am J Obstet Gynecol*. 2005;193(1):30-35.
9. Bosse K, Rhiem K, Wappenschmidt B, et al. Screening for ovarian cancer by transvaginal ultrasound and serum CA125 measurement in women with a familial predisposition: a prospective cohort study. *Gynecol Oncol*. 2006;103(3):1077-1082.
10. Kauff ND, Hurlley KE, Hensley ML, et al. Ovarian carcinoma screening in women at intermediate risk: impact on quality of life and need for invasive follow-up. *Cancer*. 2005;104(2):314-320.
11. Chiaffarino F, Parazzini F, Bosetti C. Risk factors for ovarian histotypes. *Eur J Cancer*. 2007;43(7):1208-1213.
12. Abenheim HA, Titus-Ernstoff L, Cramer DW. Ovarian cancer risk in relation to medical visits, pelvic examinations and type of health care provider. *CMAJ*. 2007;176(7):941-947.
13. Neesham D. Ovarian cancer screening. *Aust Fam Physician*. 2007;36(3):126-128.
14. Szucs TD, Wyss P, Dedes KJ. Cost-effectiveness studies in ovarian cancer. *Int J Gynecol Cancer*. 2003;13(suppl 2):212-219.
15. Bast RC. Early detection of ovarian cancer: new technologies in pursuit of a disease that is neither common nor rare. *Am Clin Climatol Assoc*. 2004;115:233-248.
16. Simon I, Liu Y, Krall KL, et al. Evaluation of the novel serum markers B7-H4, Spondin 2, and DcR3 for diagnosis and early detection of ovarian cancer. *Gynecol Oncol*. 2007;106(1):112-118.
17. Kobayashi H, Ooi H, Yamada Y, et al. Serum CA125 level before the development of ovarian cancer. *Int J Gynaecol Obstet*. 2007;99(2):95-99.
18. Kurjak A, Prka M, Arenas JM, et al. Three-dimensional ultrasonography and power Doppler in ovarian cancer screening of asymptomatic peri- and postmenopausal women. *Croat Med J*. 2005;46(5):757-764.