In 2005, more than 22,000 American women were diagnosed with ovarian cancer and 16,000 women died from the disease. The five-year relative survival rate for stage III and IV disease is 31%, and the five-year relative survival rate for stage I is 95%. Early diagnosis should lower the fatality rate. Unfortunately, early diagnosis is difficult because of the physically inaccessible location of the ovaries, the lack of specific symptoms in early disease, and the limited understanding of ovarian oncogenesis. Screening tests for ovarian cancer need high sensitivity and specificity to be useful because of the low prevalence of undiagnosed ovarian cancer. Because currently available screening tests do not achieve high levels of sensitivity and specificity, screening is not recommended for the general population. The theoretical advantage of screening is much higher for women at high risk (such as those with a strong family history of ovarian cancer and those with BRCA 1 or BRCA 2 mutations). However, even for women at high risk, no prospective studies have shown benefits of screening. The public health challenge is that 90% of ovarian cancer occurs in women who are not in an identifiable high-risk group, and most women are diagnosed with advanced-stage disease. Currently available tests (CA-125, transvaginal ultrasound, or a combination of both) lack the sensitivity and specificity to be useful in screening the general population. Ongoing clinical trials are assessing whether new tumor markers, including those generated by proteomic and genomic studies, will prove useful.

At a Glance

✦ Most ovarian cancer is diagnosed at stage III or IV in women who are not identified as being at high risk for the disease.
✦ Early diagnosis is difficult because of the inaccessibility of the ovaries for screening and the vague symptoms of early-stage disease.
✦ Screening is not recommended for the general population because of the high number of false negatives and false positives generated by currently available tests. However, new tumor markers and proteomic analysis are being studied for ovarian cancer screening.

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frequent urination; and dull back pain. Late signs and symptoms include anorexia, nausea, vomiting, increased abdominal girth, decreased weight, ascites, and persistent abdominal or pelvic pain (Harris, 2002). Often, the symptoms are attributed to gastrointestinal disturbances, psychosomatic illness, or aging. Unexplained, persistent symptoms must receive proper investigation (Luce, Dow, & Holcomb, 2003).

**Ovarian Cancer Screening and Risk**

Considering the characteristics of ovarian cancer and current screening technologies, healthcare professionals must decide whether screening is reasonable and, if so, who should be screened. The lifetime risk of developing ovarian cancer for American women is 2% (Urban, 2003). The low incidence of ovarian cancer, the lack of specificity of screening methods, and the invasive nature of follow-up required for definite diagnosis conspire to make routine screening for the general population inadvisable (Cuzick, 1999; Jacobs, 2003; Lee, 2000; Woodman, 1999). Consequently, the U.S. Preventive Services Task Force, American Cancer Society, American College of Obstetrics and Gynecology, and Canadian Task Force on Preventive Health Care agree that routine screening for ovarian cancer in the general population is not recommended (U.S. Preventive Services Task Force, 2004).

However, definable populations of women have a risk of ovarian cancer that is considerably above average and may benefit from screening tests. Risk factors for ovarian cancer include a personal history of breast cancer, a family history of ovarian cancer in first- and second-degree relatives, and certain genetic mutations such as BRCA 1 and BRCA 2, Lynch II syndrome, and Li-Fraumeni syndrome. Although lifetime risk in the general population is only 2%, high-risk populations have a lifetime ovarian cancer risk of 11%–65% (Hensley et al., 2003; Lee, 2000; Modugno & the Ovarian Cancer and High-Risk Women Symposium Presenters, 2003; Wenham et al., 2002) Additionally, Dibble, Roberts, Robertson, and Paul (2002) showed an increased prevalence of risk factors for ovarian cancer among lesbian women. The finding was believed to be related to increased body mass index as well as the presence of fewer protective factors such as pregnancy and oral contraceptive use among lesbian women. Although no clinical trials have been conducted to show the benefits of screening in high-risk populations, several authori-

**Advantages**
- Early-stage treatment yields improved outcomes.
- Presence of genetic mutations makes high-risk groups identifiable.

**Disadvantages**
- No identifiable asymptomatic period exists.
- The population overall has a low incidence rate.
- The sensitivity and specificity of current screening tests are inadequate to yield sufficient positive predictive value.
- The anatomic position of the ovaries does not allow access without invasive procedures.

**New Tumor Markers in Ovarian Cancer**

Several new markers are under investigation for potential use with CA-125 as a panel for ovarian cancer screening. Two show particular promise. The first is macrophage-colony-stimulating factor (M-CSF), a hematopoietic cytokine. The second is a combination of various lysophosphatidic acids (LPA) (Xu et al., 1991, 1998).

M-CSF has been shown to be elevated in 68% of patients with known ovarian cancer. However, the presence of elevated M-CSF is not restricted to ovarian malignancy or even malignancy in general. It also is elevated in several nonmalignant conditions, including renal disease, acute infection, pulmonary disease,
autoimmune disease, and liver disease. Additionally, M-CSF is elevated in other malignancies, including breast, lung, colon, endometrial, and cervical cancers. Somewhat compensating for the problems with the test is the fact that no definite relationship has been found between M-CSF and CA-125. The tests are complementary. Fifty-six percent of patients with clinically evident disease and normal CA-125 levels had elevated levels of M-CSF. Additionally, among 29 patients who had occult disease identified surgically and normal CA-125 levels, 9 (31%) had elevated M-CSF (Xu et al., 1991). When M-CSF is used in combination with CA-125, 96%–98% of cases are identified, including 81% of early-stage cancers. Although the sensitivity of the combination is impressive, the specificity is dismal, with 20% of women without cancer exceeding at least one threshold measurement (Suzuki et al., 1993).

LPA has sensitivity in advanced disease of 100% and in early-stage disease of almost 90%. In an ovarian cancer study involving healthy controls, women with benign gynecologic disease, and women with other malignancies, LPA was significantly elevated in 9 of 10 women with stage I ovarian cancer and all of the 24 women with stage II, III, or IV disease. LPA has sensitivity for other gynecologic cancers as well. LPA was elevated in 35 of 36 patients with other gynecologic malignancies. The specificity for ovarian cancer and primary peritoneal cancer was 87%; the overall specificity for gynecologic (cervical, endometrial, ovarian, and peritoneal) malignancies was 90% (Xu et al., 1998).

Additional markers under investigation include mesothelin, α folate receptor, and OVX1. The use of a panel of markers also holds promise as a screening strategy (Urban, 2003; Whitehouse & Solomon, 2003).

**Ultrasound in Screening**

The other major modality being tested for benefit in ovarian cancer screening is ultrasound. One study (van Nagell et al., 2000) of annual transvaginal sonography (TVS) involving almost 15,000 asymptomatic women achieved a sensitivity of 81% and a specificity of 98%. Unfortunately, although TVS was quite accurate in identifying abnormal ovarian volume and morphology, it could not reliably distinguish between benign and malignant lesions. As a result of the screening study, 180 patients underwent laparoscopy or laparotomy to diagnose 17 cancers, yielding a positive predictive value of 9.4%. TVS was able to detect early-stage disease. Of the 17 cancers detected, 11 were stage I, 3 were stage II, and 3 were stage III. Unfortunately, four patients developed ovarian cancer within 12 months of a negative screen. Two of them had disease progression from normal ovaries to stage III disease in 12 months. The other two had metastatic disease with normal ovarian volumes. The cases suggest that the apparent benefit of the screening method may be caused by length bias (Fields & Chevlen, 2006; van Nagell et al.).

Similarly, a Japanese study (Sato, Yokoyama, Sakamoto, Futagami, & Saito, 2000) involving TVS of 183,000 asymptomatic women demonstrated an increase in diagnosis of early-stage disease, with 77% of cancers being diagnosed at stage I. Before the study, 56% of all cases of ovarian cancer at the institution were stage III and IV. Because of the large number of stage I ovarian cancers diagnosed through the study, the percentage of patients with stage I ovarian cancer rose from 30% to 59%.

Just as efforts have been made to improve the efficacy of CA-125 as a screening test, so, too, have improvements in ultrasonography been used to achieve greater diagnostic accuracy. Another study (Kurjak, Kupesic, Sparac, Prka, & Bekavac, 2003) was undertaken to determine the diagnostic accuracy of three-dimensional (3-D) sonography and 3-D power Doppler imaging compared to standard two-dimensional (2-D) imaging. Over a six-year period, all patients with suspected ovarian or adnexal lesions underwent four sonographic examinations the week before surgery. Of the 43 stage I cancers diagnosed, 70% were detected by 2-D grayscale sonography and 86% were detected by combined 2-D grayscale and color Doppler sonography. Use of 3-D sonography alone had a diagnostic rate of 74%. Analysis of vascular architecture with 3-D power Doppler detected 95% of the cases. Combined 3-D sonography and 3-D power Doppler findings reached an impressive diagnostic rate of 98% of stage I ovarian malignancies. However, the study was performed in a select population of women scheduled for surgery to rule out ovarian cancer. A follow-up study by Kurjak et al. is being conducted in Croatia. The researchers plan to enroll 10,000 asymptomatic women during a five-year period.

**Multimodal Screening**

To date, the most successful results have been obtained from studies using a multimodal approach, combining CA-125 with ultrasonography rather than using either test alone. Jacobs et al. (1999) conducted a randomized, controlled pilot study of ovarian cancer screening in the United Kingdom involving 22,000 women. The screened group was offered three annual CA-125 serum tests. If CA-125 was 30 U/ml or greater, subjects received 3-D pelvic ultrasonography. Overall, 468 women underwent 781 ultrasound scans because of CA-125 elevation. Of the 468 women, 29 had abnormal sonograms and underwent surgical investigation. The specificity of ultrasound to detect structural abnormalities of the ovary was almost 100%, but its specificity to detect ovarian cancer was far less. Six of the 29 women proved to have cancer (20.7% positive predictive value). An additional 10 women in the screened group developed ovarian cancer during the seven-year follow-up portion of the study. A total of 20 women from the control group developed ovarian cancer. Median survival for the patients with cancer from the screened group was 72.9 months; it was 41.8 months for the patients with cancer from the control group, but the finding did not achieve statistical significance (Jacobs et al.). Stage at diagnosis was similar in both groups, but the control group had significantly more high-grade malignancies than the screened group. Further studies are needed to confirm the findings (Jacobs et al.).

Ongoing randomized clinical trials using a multimodal screening approach include the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial and the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). The PLCO trial has completed its enrollment of 74,000 women aged 55–74. The women were randomized to control and screening arms. The UKCTOCS started recruitment in 2001. It plans to
include 200,000 postmenopausal women randomized to one of three groups: control, ultrasound screening, or multimodal screening. In addition to examining the efficacy of the screening modalities, the study also will address the issues of health economics, adherence to screening, target population, stress related to screening, and physical morbidity (Menon & Jacobs, 2002).

On the Horizon

Proteomics is a new and exciting area on the horizon in ovarian cancer screening. It is the branch of genetics that studies the full set of proteins encoded by a genome. The idea behind proteomics is to compare the types and amounts of proteins in the sera of women known to be disease-free with those of women known to have ovarian cancer. The thinking is that differences in specific proteins may help to identify early-stage disease. Initial promising results were reported by the U.S. Food and Drug Administration and National Institute of Health Clinical Proteomic team in 2002. Petricoin et al. (2002) used sera from 50 women with ovarian cancer and 50 unaffected women as a training set. The researchers were able to identify five protein peaks in the ovarian cancer group that were not present in the unaffected group. The proteomic pattern completely discriminated cancer from noncancer. The identified pattern then was used to analyze 116 masked serum samples—50 from women with ovarian cancer and 66 from unaffected women and women with benign disorders. The established pattern correctly identified all 50 ovarian cancer cases, 18 of which were stage I. Sixty-three of the 66 nonmalignant samples were identified correctly. In the admittedly small sample, the test exhibited a sensitivity of 100%, specificity of 95%, and positive predictive value of 94% (Petricoin et al.). Of course, the high positive predictive value was in a highly preselected population that had an ovarian cancer prevalence of almost 50%.

The results of the proteomic study were greeted with excitement and enthusiasm, perhaps in excess of what was warranted by the data. Plans were made to market the test under the brand name OvaCheck® (Correlogic Systems, Inc., Bethesda, MD; Quest Diagnostics Incorporated, Lyndhurst, NJ; and Laboratory Corporation of America, Burlington, NC). It currently is under review by the U.S. Food and Drug Administration to determine the appropriate regulatory path. The test is expected to become commercially available when the process is completed. Currently, it is available only in research setting.

Some questions have been raised regarding the test. When applied to the nonmalignant study population, it performed with a specificity of 95%, but its specificity in the general population is unknown (Lafky & Maihle, 2002). Additionally, a specificity of 95% is inadequate for ovarian cancer screening in the general population because of the low prevalence of asymptomatic disease. Specificity greater than 99% is necessary to achieve the target positive predictive value of 10%. Perhaps the specificity of the test may reach acceptable levels as the data set grows, but that is not a certainty (Daly & Ozols, 2002).

However, the most serious questions regarding the Petricoin et al. (2002) report were raised concerning the reliability and reproducibility of the results using the same data sets as those used in the initial study. In separate, independent studies, Sorace and Zhan (2003) and Baggerly, Morris, and Coombes (2004) found bias between the data sets, which may have been caused by artifact (extraneous signals that did not arise from the specimen itself) rather than the biology of cancer. Baggerly et al. examined all three data sets and were unable to reproduce the results across the experiments. Sorace and Zhan examined the third data set and found a significant nonbiologic experimental bias between the cancer and noncancer groups. This calls into question the validity of the data set for demonstrating patterns of reproducible diagnostic value.

Because of the questions posed regarding the reliability of the initial findings, the Society of Gynecologic Oncologists (2004) recently reviewed all published work regarding OvaCheck and concluded that additional research is necessary before the test is made available to the public. Despite initial stumbling, further developments of proteomic testing hold promise to improve the early detection of ovarian cancer.

Conclusions

Although the goal of successful screening for ovarian cancer remains elusive, a foundation has been laid and researchers have a clearer understanding of the criteria by which they must judge putative breakthroughs in the field. Until improvements in test specificity, sensitivity, and positive predictive value are made (see Table 1), healthcare professionals must screen individuals at high risk for ovarian cancer, if at all, with a keen awareness of the shortcomings of screening tests.

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