Are Serum Protein Biomarkers Effective in Detecting Ovarian Cancer in Its Early Stages?

Yvonne Leahy, RN

September is National Ovarian Cancer Month (American Cancer Society, 2009). Ovarian cancer accounts for the highest number of gynecologic deaths and the fifth highest number of cancer deaths in American women (Jemal et al., 2008). Approximately 21,550 women living in the United States will be diagnosed with cancer of the ovaries in 2009 (Horner et al., 2009). The Surveillance, Epidemiology, and End Results cancer database shows that the five-year relative survival rate for ovarian cancer is approximately 45.9% (Horner et al.). Regarding stage distribution for all cases of ovarian cancer, metastatic disease is diagnosed in about 62% of cases, whereas localized and regional disease is diagnosed in 15% and 17% of cases, respectively (Horner et al.).

Because early-stage ovarian cancer presents with nonspecific symptoms, diagnosis most often is made after the malignancy has spread beyond the ovaries (O’Rourke & Mahon, 2003). Mortality rates for this type of malignancy are high because of a lack of an early-stage screening method (Visintin et al., 2008). The 10-year survival rate for localized ovarian cancer is approximately 90%. It drops significantly to about 60% for regional disease and about 20% for metastatic disease. This is the basis for continued research efforts to obtain high-quality screening techniques for early detection of ovarian cancer (Chambers & Vanderhyden, 2006).

Because of a low prevalence of ovarian cancer in U.S. women, an ovarian cancer diagnostic or screening test must have a minimum of 99.6% specificity before it can be used routinely in the general population of postmenopausal women (Jacobs & Menon, 2004). Such a test may offset potential morbidity and mortality, which can be associated with complications of surgery for patients who have false-positive ovarian cancer screening tests (Jacobs & Menon). See Figure 1 regarding clinical uses of a diagnostic tool. An ovarian cancer screening test also should have high sensitivity (i.e., positive test in women with the disease) and a suitable positive predictive value (PPV) (O’Rourke & Mahon, 2003). PPV is the likelihood that a person has a particular disease when he or she has a positive test result for that disease. Negative predictive value (NPV) is the likelihood that a person does not have a particular disease when he or she has a negative test result for that disease (Visintin et al., 2008).

Current Screening Methods

Routine screening for ovarian cancer in the general population is not recommended (U.S. Preventive Services Task Force, 2005) because traditional screening methods are not sensitive and specific enough (Nossov et al., 2008). The workup for women who have signs and symptoms suggestive of ovarian cancer may include abdominal and pelvic examination, ultrasound, abdominal and pelvic computed tomography, cancer antigen 125 (CA-125) testing, laparotomy (National Comprehensive Cancer Network, 2008), and laparoscopy. Signs and symptoms are as follows (National Comprehensive Cancer Network).

- Suspicious pelvic mass palpable on physical examination
- Ascites and abdominal distention
- Symptoms (e.g., bloating, abdominal or pelvic pain, eating difficulty, feeling full quickly after eating, urinary symptoms such as urgency or frequency) not indicative of another malignancy
- Women who are at high risk for developing ovarian cancer (i.e., family history of ovarian or breast cancer or history of breast cancer) sometimes undergo transvaginal ultrasound (Jacobs & Menon, 2004).

Proteomics

Proteomics is the complex study of the human proteome, which consists of a dynamic wide range of individual proteins. Proteomic technology has the potential to help develop diagnostic tools for the detection of cancer. Since the turn of the century, a number of techniques have emerged for identifying and characterizing proteins (Jacobs & Menon, 2004). The technologies are advantageous because...

Yvonne Leahy, RN, volunteers for the Canadian Cancer Society in Stirling, Canada. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Clinical Journal of Oncology Nursing or the Oncology Nursing Society.

Digital Object Identifier: 10.1188/09.CJON.443-445
they now can identify several potential biomarkers in a small serum sample. Someday, biomarkers may be helpful in diagnosing early-stage disease and monitoring recurrence of disease (Nossov et al., 2008). See Table 1 for a proposed guide for the creation of a protein biomarker. Originally, new biomarkers were identified with cells or tissues from patients with cancer versus healthy controls. More recently, biomarkers are identified with serum or urine samples of those two groups (Gagnon & Ye, 2008). Human serum is a protein-rich environment and, therefore, is well suited for detecting biomarkers in clinical proteomics. “Cancer is a product of the proteomic tissue microenvironment” (Calvo, Petricoin, & Liotta, 2005, p. 67).

### Table 1. Proposed Guide for the Creation of a Protein Biomarker

<table>
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<th>STAGE</th>
<th>OBJECTIVE AND DETAILS</th>
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<tr>
<td>Discovery</td>
<td>To include any analysis that yields one or more viable protein or peptide biomarkers whose molecules are categorically identified</td>
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<tr>
<td>Verification and validation</td>
<td>To measure identified molecules in large sample sets to determine key parameters (e.g., sensitivity and specificity in relation to a disease) for a diagnostic test To verify biologic importance and validate prototype assays for biomarkers To verify and validate data by more than one technology platform (e.g., provide uniformity across laboratories), which are open for ongoing statistical analysis</td>
</tr>
<tr>
<td>Clinical implementation</td>
<td>Must be inexpensive and relatively noninvasive Depends on factors such as disease prevalence, treatment availability, cost, and compatibility with existing laboratory instrument platforms (e.g., a biomarker panel of five proteins or fewer collectively, could be implemented into existing laboratory immunoassays) Is costly and time consuming if new instrument platform needs to be developed</td>
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Note. Based on information from Anderson, 2005; Gagnon & Ye, 2008.

### Evidence for Use of Serum Protein Biomarkers

A group of researchers, mostly from Yale University School of Medicine in New Haven, CT, used a novel serum test consisting of six protein biomarkers collectively to detect ovarian cancer (Visintin et al., 2008). The study group consisted of 156 patients newly diagnosed with ovarian cancer (i.e., preoperative) and 362 healthy controls. Serum samples were collected from 2002–2006. See Table 2 for individual characteristics and uses of the six biomarkers. In the study, about 75% of the patient group had advanced (i.e., stage 3 or 4) ovarian cancer and about 25% had early-stage (i.e., stage 1 or 2) disease. The performance of the six-biomarker serum test was studied in a test population (i.e., blinded cohort) to determine whether the diagnostic test could differentiate ovarian cancer samples from control samples. Complex quantitative analysis of the six protein biomarkers included the use of two platforms. See Table 3 for characteristics for the two platforms.

Results supported that the six-biomarker serum test can distinguish between women with and women without ovarian cancer with a sensitivity of 95.3% and specificity of 99.4%. The PPV and NPV for the test population were 99.3% and 99.2%, respectively. The serum test delineated early-stage ovarian cancer with 91.6% sensitivity. This is significantly higher than the sensitivity for CA-125 (i.e., less than 60%) (Jacobs & Menon, 2004), which is the only other biomarker available for diagnosing ovarian cancer. Individually, the six biomarkers did not sufficiently separate the ovarian cancer samples from healthy control samples. Although the actual values for each biomarker differed in the two platforms, the trend differentiating the presence or absence of ovarian cancer was retained (Visintin et al., 2008).

A similar serum test (i.e., consisting of four biomarkers listed in Table 2) was used by Mor et al. (2005). It diagnosed new ovarian cancer cases and recurrent disease with a sensitivity of 95% (i.e., 5% false negatives) and a specificity of 95% (i.e., 5% false positives). Two other retrospective studies, whose researchers were mainly from Johns Hopkins Medical Institutions in Baltimore, MD, or the University of California, Los Angeles, used four serum biomarkers to detect early-stage ovarian cancer (Nossov et al., 2008). The two studies diagnosed the malignancy with sensitivity (i.e.,

### Table 2. Individual Characteristics and Uses of Six Biomarkers

<table>
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<tr>
<th>BIOMARKER</th>
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<tr>
<td>CA-125</td>
<td>Not related to normal physiology of ovaries Approved for monitoring treatment response and progression of ovarian cancer Most commonly used biomarker for diagnosing epithelial ovarian cancer Is elevated in 82% of women with advanced epithelial ovarian cancer</td>
</tr>
<tr>
<td>IGF-IIa</td>
<td>Acts as a mediator of gonadotropin action in the human ovary</td>
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<tr>
<td>Leptin*</td>
<td>May be linked to hypothalamic gonadotropin-releasing hormone secretion Levels may be affected by timing of serum collection in relation to disease onset</td>
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<tr>
<td>MIF</td>
<td>Is a proinflammatory cytokine (i.e., protein) that regulates inborn and modified immune responses in biologic processes (e.g., tumor growth, progression) Not related to normal physiology of ovaries Mean levels are much higher (i.e., p &lt; 0.001) in patients with ovarian cancer compared to healthy women.</td>
</tr>
<tr>
<td>Osteopontin*</td>
<td>Mean serum levels are higher (i.e., p &lt; 0.01) in patients with ovarian cancer compared to healthy women. Specificity of osteopontin predicting ovarian cancer is 54.7% but increased to 87.4% when both osteopontin and CA-125 levels were elevated in the same patient.</td>
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<tr>
<td>Prolactin*</td>
<td>Inhibits progesterone secretion in early stages of ovarian follicular growth Enhances progesterone secretion in the ovarian luteal phase</td>
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* Biomarkers used collectively for detecting ovarian cancer in Mor et al.’s (2005) study

CA-125—cancer antigen 125; IGF-II—insulin-like growth factor II; MIF—macrophage inhibitory factor

Note. Based on information from Agarwal et al., 2007; Bachelot & Binart, 2005; Gagnon & Ye, 2008; Giudice, 2001; Mor et al., 2005; Nakae et al., 2006; Popovic & Casanueva, 2002; Visintin et al., 2008.
Improvements have been made in the surgical and chemotherapeutic management of ovarian cancer (Jacobs & Menon, 2004). Significant progress also has been made in understanding its pathophysiology. However, that has not rendered improved survival rates. Prospective investigation using serum protein biomarker(s), which has shown high sensitivity and specificity for diagnosing ovarian cancer, has the potential to advance early detection and improve morbidity and mortality for the disease (Nossov et al., 2008). Because of the complex nature of ovarian cancer, researchers presume that more than one biomarker will be required to detect all stages and types of the malignancy. Sharing of information among researchers may lead to faster discovery, validation, and approval of biomarkers for ovarian cancer screening (Gagnon & Ye, 2008).

To date, no evidence-based test is available for detecting ovarian cancer in its early stage (Nossov et al., 2008). Continued cooperative efforts by international researchers to develop new tests or further evaluate existing noninvasive tests (e.g., use of single or multiple biomarkers) for early detection of ovarian cancer is critical (National Cancer Institute, 2009). Women's active participation in clinical trials that study such screening methods has the ultimate potential for saving lives.

Author Contact: Yvonne Leahy, RN, can be reached at leahy_6@yahoo.ca, with copy to editor at CJONEditor@ons.org.

References


