

## Early Detection of Ovarian Cancer

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### Introduction

Ovarian carcinoma is the fourth leading cause of cancer-related death in women in the United States. In 1995 it is estimated that 26,600 new cases will be diagnosed in the United States and 14,500 deaths will occur.<sup>1</sup> Despite advances in medical and surgical treatment, attempts at early diagnosis, and a clearer picture of the etiology of this disease, increases in long-term survival have been small. According to data from the Surveillance, Epidemiology, and End Results program, from 1973 to 1991 the five-year survival of patients with ovarian cancer increased from 36 percent to only 42 percent.<sup>1</sup> In the past 15 years, any decrease in overall mortality of patients with ovarian cancer may be directly attributable to the excellent survival for the 1,400 patients diag-

nosed annually with ovarian germ-cell tumors. Unfortunately, most patients with epithelial ovarian cancer display a paucity of symptoms and are most often diagnosed with advanced-stage disease at the time of initial presentation and treatment. Seventy percent of patients present initially with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV disease (Table 1). At best this group of patients will have a five-year survival in the range of 15 to 20 percent despite aggressive treatment. In contrast, the minority of patients who present with FIGO stage I disease have a five-year survival in the range of 80 to 90 percent.<sup>2-4</sup>

In most situations, patients are diagnosed with early-stage ovarian cancer because they have undergone surgical exploration for a clinically detected physical abnormality with no other reliable indicator of disease status. Although cure of disease when diagnosed at an early stage is possible in most cases, historically, the only tool for detection of early forms of ovarian cancer has been the pelvic examination. The poor survival of patients with advanced-stage disease, where detection also occurs principally by history and physical examination, makes it clear that additional methods are needed for earlier detection of ovarian cancer where the potential for cure is greatly enhanced.

This review will discuss the issue of early detection of ovarian cancer and highlight the pathologic problems, statistical considerations, the diagnostic mo-

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**Table 1**  
**FIGO Staging System for Ovarian Cancer**

<b>Stage I</b>	Growth limited to the ovaries
IA	Growth limited to one ovary; no malignant ascites. No tumor on the external surface; capsule intact
IB	Growth limited to both ovaries; no malignant ascites. No tumor on the external surface; capsule intact
IC	Either IA or IB but with tumor on the surface of one or both ovaries, or with capsule ruptured, or with malignant ascites, or positive peritoneal cytology
<b>Stage II</b>	Growth involving one or both ovaries with pelvic extension
IIA	Extension and/or metastasis to the uterus and/or tubes
IIB	Extension to other pelvic tissues
IIC	Tumor either IIA or IIB but with tumor on the surface of one or both ovaries, or with capsule(s) ruptured, or with malignant ascites, or positive peritoneal cytology
<b>Stage III</b>	Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum
IIIA	Tumor limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIB	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative
IIIC	Abdominal implants greater than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes
<b>Stage IV</b>	Growth involving one or both ovaries with distant metastasis. If pleural effusion is present, there must be a positive cytologic test to allot a case to stage IV. Parenchymal liver metastasis equals stage IV

FIGO = International Federation of Gynecology and Obstetrics

dalities available for screening detection, and the major clinical applications that have been undertaken using currently available technology.

### The Pathologic Entity

Cancer of the ovary is a collection of diverse pathologic entities that can be broadly characterized as epithelial, germ cell, or stromal in origin. By far the most common forms of ovarian carcinoma are the epithelial malignancies, which account for greater than 80 percent of reported cases.<sup>5</sup> Epithelial ovarian carcinoma is further divided into different cell types based on histologic similarities to normal genital and urologic tissues. Additionally, a related disease is described, papillary serous carcinoma of the peritoneum, which is histologically identical

sarily discriminate between the various forms of ovarian cancer, especially when these technologies are broadly applied to the general population. In this setting a variety of possible diagnoses can be obtained, including nonovarian pathologic entities such as endometriosis, pelvic inflammatory disease, uterine leiomyoma, metastatic tumors, and pregnancy.

The identifiable presence of a premalignant lesion may improve the effectiveness of an early-detection screening program. In the case of ovarian cancer, an unequivocal premalignant lesion is lacking, at least from a clinical standpoint. Similarly, although there is an accumulating body of knowledge regarding the genetic lesions observed in ovarian cancer, the molecular pathogenesis of early ovarian neoplasia remains unclear. Nevertheless, anatomic lesions of the ovary (i.e.,

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to primary serous carcinoma of the ovary, but is suspected to have a multifocal origin from the epithelial lining of the peritoneal cavity.

A clinically distinct, intermediate form of epithelial ovarian carcinoma also exists, the ovarian tumor of low malignant potential (LMP). These tumors retain an overall cellular and nuclear architecture similar to invasive carcinomas and have the ability to metastasize, but lack the invasive histologic properties of their fully malignant counterparts. At all stages of disease, LMP tumors are associated with an excellent prognosis.<sup>5,6</sup>

From a practical standpoint, early detection of ovarian cancer is focused primarily on epithelial malignancies. It should be emphasized, however, that screening methodologies do not neces-

sarily discriminate between the various forms of ovarian cancer, especially when these technologies are broadly applied to the general population. In this setting a variety of possible diagnoses can be obtained, including nonovarian pathologic entities such as endometriosis, pelvic inflammatory disease, uterine leiomyoma, metastatic tumors, and pregnancy.

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The existence of a cystic ovarian neoplasm identified through clinical means combined with the observation that both benign and malignant epithelium often coexist within the same malignant lesion has led to the widely held assumption that the premalignant or early malignant phase of disease includes the formation of a complex cystic ovarian lesion.<sup>7,8</sup> This assumption has been challenged recently by the description of small-volume malignant disease in otherwise normal-sized ovaries.<sup>9</sup> In the absence of any other anatomic or genetic lesion, however, the identification of a complex cystic lesion and the identification of associated biochemical or genetic

abnormalities have been the focus of contemporary early-detection studies. It cannot be emphasized enough, however, that the detection of ovarian cancer early in the disease process is, in part, hampered by a general lack of knowledge regarding the pathogenesis of ovarian cancer.

### **Biostatistical Considerations**

The effectiveness of a detection program for early-stage cancer depends on the disease for which screening is undertaken and the characteristics of the study modality. Several criteria need to be satisfied in the design and clinical application of an early-detection program. As mentioned previously, an ideal early-detection

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strategy requires that the disease has an identifiable phase of early invasive disease, such that the outcome of patients is improved if the disease is detected at an early stage. The disease itself must also pose a significant medical threat to justify the expense and effort of a population-based screening program. The testing modality should be sensitive enough to detect small-volume disease states. Importantly, specificity must be maintained so that individuals without disease can be accurately identified. High specificity becomes especially important in ovarian cancer screening because major operative procedures are often required to confirm or dispute the results of the screening procedure. Effective early-detection programs also require that the testing modality be cost efficient, relatively easy to perform, and widely available for use. The extent to which the disease and detection

methods meet these criteria will determine the effectiveness of the screening program.

In reviewing the results of any screening trial in ovarian cancer, the issue of study bias and the presence or absence of a control group needs to be addressed before any final recommendations for screening can be made. Selection bias can occur when the population under study does not truly represent the population as a whole. In the absence of a randomized trial or examination of a very large study group, selection bias is an important limiting factor of any study.

Lead time bias can occur when the screening procedure simply advances the date of diagnosis without affecting survival or outcome. In ovarian cancer, the detection of patients with advanced-stage disease during the screening process would not necessarily lead to enhanced survival. In this setting the expense and effort of screening may not be justifiable to identify a small number of patients for whom effective treatment is limited.

Length time bias can occur when the disease state, diagnosed as a result of the screening process, is nonvirulent or of such an indolent nature that early diagnosis does not alter the natural history of the disease. In ovarian cancer screening, length time bias may be manifest by the diagnosis of intermediate forms of malignancy such as LMP tumors of the ovary.

Finally, the presence or absence of an appropriate control is necessary to determine the applicability of any screening method for routine use. In uncontrolled studies it is difficult to assess cost effectiveness or the impact of screening on disease-specific mortality.

Ovarian cancer meets the criteria of a disease for which screening can be justified. Clearly, the disease is lethal to most patients so diagnosed. Effective treatment for early-stage disease also exists, such that early detection in most patients could be expected to favorably affect long-term survival. A special concern rel-

evant to the detection modality, however, can be identified and relates to the prevalence of the disease. Ovarian cancer has a prevalence of about 50 per 100,000 and an annual incidence of 14 per 100,000.<sup>1,9</sup> In the absence of a family history of ovarian cancer, the lifetime risk of developing the disease is one in 70, in contrast to breast cancer where the lifetime risk is one in nine. In a disease with a relatively low prevalence such as ovarian cancer, the specificity of the testing modality is critical. For example, assuming that a screening procedure has a sensitivity of 80 percent, a specificity of 98 percent would potentially result in 50 surgical procedures for every cancer diagnosis.<sup>4</sup> Because of the expense and patient morbidity that would accompany an excessive

in the screening of early ovarian cancer has been the postmenopausal palpable ovary syndrome.<sup>10</sup> In this usage, any palpable ovary in a postmenopausal patient was considered abnormal because a senescent ovary should not be detectable by palpation. This type of physical finding, as an indication for operative diagnosis, has never been validated. As might be expected, interobserver variability is considerable. Compared with the use of modern technologies, such as ultrasound and computed tomographic scanning, physical examination is often inadequate for the detection of grossly abnormal ovaries. When used alone, physical examination lacks the necessary sensitivity for use in the screening detection of ovarian cancer.<sup>11</sup>

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number of confirmatory operative procedures, the specificity of the testing modality must approach 100 percent.

### **Detection Modalities**

A number of commonly available and experimental techniques may be useful in the screening detection of ovarian cancer. There is little doubt that additional modalities will become available as the technology of diagnostic imaging advances and the etiology and molecular biology of ovarian cancer are elucidated in the years ahead. The following synopsis is not meant to be inclusive.

#### **HISTORY AND PHYSICAL EXAMINATION**

Historically, the basic tools for the diagnosis of ovarian cancer have been the history and physical examination. The most notable use of the physical examination

A carefully elicited family history on the other hand is an important tool in the identification of the individual at increased risk for the development of ovarian cancer. Several hereditary family cancer syndromes that involve ovarian neoplasms have been identified (Table 2). For instance, the risk of developing either breast or ovarian cancer for the unaffected members of families with the hereditary breast/ovarian cancer syndrome can be exceptionally high, ranging up to 82 percent by 70 years of age.<sup>12</sup>

When considered together, however, patients with hereditary forms of epithelial ovarian cancer will account for only a small fraction of all cases diagnosed on an annual basis. About 95 percent of cases of ovarian cancer are sporadic in nature with no discernible pattern of inheritance. For the individual without a family history of an identifiable syndrome, the risk varies depending on

the number of sporadic cases identified in the family and ranges from 1.4 percent (no affected relatives) to five percent (one affected relative) to seven percent (two affected relatives).<sup>13</sup> Although the differences in lifetime risk for the development of ovarian carcinoma in families with and without a familial cancer syndrome are considerable, from a clinical standpoint perhaps the greater risk is failing to identify families with a hereditary ovarian cancer syndrome.

Although history alone cannot be used to reliably predict the onset of disease, a positive family history clearly identifies a subpopulation of individuals at heightened risk for the development of disease who might benefit from frequent surveillance and/or prophylactic operative intervention at an earlier age.<sup>13,14</sup> Although there have been several studies that highlight the potential benefit of prophylactic oophorectomy, the individual patient should be cautioned that operative measures do not address the potential future risk of papillary serous carcinoma of the peritoneum.<sup>15</sup>

#### IMAGING MODALITIES.

Several modalities exist for the imaging of both normal and abnormal ovaries, including ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), radioimmunoscinotography, and a newer modality, positron-emission tomography (PET) scanning. Of these, ultrasonography has received the greatest attention as a screening tool. Over the past decade, the evolution of ultrasound technology has progressed at a rapid pace. High-frequency vaginal transducers and other hardware and software improvements now permit high-resolution images of ovarian and endometrial pathology. At the present time, transabdominal and transvaginal sonography (TVS) are widely available for diagnostic use and offer a cost advantage over any other imaging modality.

Transabdominal ultrasonography offers the advantage of simultaneous evaluation of other abdominal and retroperitoneal structures in conjunction with the pelvis. As such, abdominal ultrasonography is a valuable tool in the evaluation of the patient with an adnexal mass. For the purpose of screening detection, the major disadvantages include the requirement for patient preparation and difficulty in distinguishing sonographically between benign and malignant ovarian tumors.<sup>16,17</sup> As opposed to TVS, the specificity and positive predictive value of the abdominal approach are unacceptably low.<sup>11</sup>

Transvaginal sonography represents a notable improvement in the ability to assess pelvic pathology. The closer proximity of a high-frequency vaginal probe to the ovary allows greater resolution of ovarian architectural detail. Decreased interobserver variability and the lack of a requirement for patient preparation are distinct advantages. The greater enhancement of ovarian imaging has allowed several investigators to develop scoring systems based on the morphologic characteristics of the ovary. Such systems based on ovarian volume, cyst wall thickness, and the presence of septae and/or papillary growths allow quantification of the ultrasound findings and can be used to systematically assess the risk of malignancy (Table 3).<sup>18,19</sup> In this usage a morphologic score is determined based on the sum of the numeric values assigned to individual sonographic findings. In practice a morphologic assessment with a total score less than five is generally associated with a pathologic finding of benign disease.<sup>8,19</sup>

Color flow Doppler imaging of adnexal lesions is another recently developed tool that can provide additional important information regarding the risk of malignancy.<sup>20</sup> This technique assesses impedance to blood flow in vessels proximate to the ovary. In ovarian neoplasms neoangiogenesis leads to the formation of

**Table 2**  
**Ovarian Neoplastic Syndromes**

<b>Syndrome</b>	<b>Associated Neoplasm(s)</b>
Gonadal dysgenesis	Gonadoblastoma, dysgerminoma
Multiple nevoid basal cell carcinoma	Ovarian fibroma
Peutz-Jeghers syndrome	Granulosa theca cell tumor
Hereditary site-specific ovarian cancer	Epithelial ovarian cancer
Hereditary breast/ovarian cancer	Breast and epithelial ovarian cancer
Lynch II (hereditary nonpolyposis colorectal cancer)	Colorectal, endometrial, breast, and epithelial ovarian cancer

abnormal vessels with a lower impedance to blood flow. Visual displays of color-enhanced blood flow patterns and calculations of impedance (i.e., pulsatile index) can be obtained simultaneously in conjunction with high-frequency TVS. This combined technique can improve specificity and enhance the ability to discriminate benign from malignant ovarian pathology.<sup>21</sup> The value of color flow Doppler imaging for the screening detection of ovarian cancer, however, remains unknown.<sup>21,22</sup>

Pelvic and abdominal CT scanning has proven utility in the management of patients with gynecologic malignancies. In ovarian cancer CT scanning provides valuable information regarding disease volume, response to therapy, diagnosis of recurrent disease, and involvement of other organ systems with disease. The ability of a CT scan to image solid lesions less than 1 to 2 cm or small cystic lesions, however, is limited.<sup>23</sup> The value of CT as a screening tool is further diminished by cost, the necessity for administration of oral and/or intravenous contrast material, and the use of ionizing radiation.

Similar to CT, MRI scanning of the pelvis is useful in assessing adnexal and

uterine pathology. MRI scanning can provide remarkably detailed visual images and has been used to distinguish between various forms of benign ovarian neoplasms.<sup>24</sup> Equipment and implementation costs, however, are prohibitive.

Positron-emission tomography is a newer technique and, although not generally available, has been used to diagnosis occult recurrent ovarian cancer.<sup>25</sup> Although prohibitively expensive, this technique is intriguing because detection does not necessarily rely on the presence of a cystic ovarian lesion. As with CT and MRI imaging, the use of PET for ovarian cancer screening is strictly investigational.

#### BIOCHEMICAL MARKERS

A number of cell-surface antigens and serum proteins are produced by ovarian tumors and can be assayed using monoclonal antibodies. Some of these assays have been applied clinically as markers of disease status and are useful in the detection of subclinical disease and in the diagnosis of recurrent ovarian cancer.<sup>26,27</sup> As such, the use of these assays in the screening detection of ovarian cancer would seem logical. However, most, if not all, of

**Table 3**  
**Morphologic Ovarian Assessment by Transvaginal Sonography**

Measurement Obtained	Score				
	0	1	2	3	4
Ovarian volume (cm <sup>3</sup> )	<10	10-50	>50-200	>200-500	>500
Cyst wall structure (mm)	<3 mm thickness	≥3 mm thickness	Papillary projection <3mm	Papillary projection ≥3mm	Solid
Internal septal structure	No septa	Thin <3 mm	Thick 3 mm – 1 cm	Solid area ≥ 1 cm	Solid

Adapted with permission from DePriest et al.<sup>19</sup>

the antigenic markers described in ovarian cancer are not unique to this disease. One of the many challenges that faces basic science research in ovarian cancer is the elucidation of a highly specific biomarker (or combinations of several biomarkers) that can be applied to screening detection.

Of the biomarkers described in ovarian cancer, CA 125 has been the most extensively studied. CA 125 is a cell-surface glycoprotein of unknown function that is detectable in 80 percent of cases of epithelial ovarian cancer.<sup>28,29</sup> This assay is commonly used clinically in the diagnostic evaluation of ovarian masses, in monitoring response to treatment, and in the follow-up evaluation of patients with ovarian cancer.

For use as a screening tool, several observations are relevant. CA 125 has been shown to be elevated prior to the clinical development of primary and recurrent ovarian cancer.<sup>30,31</sup> In those patients with early-stage disease, however, CA 125 is elevated in less than half of the cases.<sup>28</sup> Further, in premenopausal patients, several benign conditions are also associated with mild elevations of CA

125. These include endometriosis, pelvic inflammatory disease, pregnancy, and leiomyoma uteri. Malignancies of the lung, breast, colon, cervix, endometrium, and pancreas have also been associated with elevated CA 125.<sup>27</sup> Interestingly, mucinous neoplasms of the ovary generally do not elaborate CA 125. Although CA 125 can be employed for the detection of malignant disease, specificity becomes an issue of concern in premenopausal patients and for those patients with mucinous tumors.

The use of other markers for detection screening of ovarian cancer has been limited despite the fact that many are known to be elevated in patients with ovarian cancer (Table 4). Of particular interest is TAG 72, which is recognized by the monoclonal antibody B72.3. This antibody has been conjugated with radionuclides with both therapeutic and diagnostic implications.<sup>32</sup> The CA 15-3 and CA 19-9 antigens are elevated in a variety of epithelial malignancies, but are used primarily in patients with known breast and pancreatic malignancies. The CA 54/61 and NB/70K antigens are both elevated in the presence of mucinous tu-

**Table 4**  
**Biologic Markers in Ovarian Cancer**

CA 125	Carcinoembryonic antigen (CEA)
CA 15-3	Lipid-associated sialic acid (LASA)
CA 54/61	Placental alkaline phosphatase (PLAP)
CA 19-9	Cancer-associated serum antigen (CASA)
TAG-72	Urinary gonadotropin fragment (UGF)
NB/70K	Ovarian serum antigen (OSA)
OVX1	Macrophage colony-stimulating factor (M-CSF)
	Human milk fat globulin (HMFG2)

mors,<sup>33,34</sup> but the role of these markers in screening for ovarian cancer would appear to be limited to combinations with other markers.

Recently, simultaneous determination of several tumor markers has been evaluated to determine whether sensitivity and specificity can be improved. CA 125 in combination with TAG 72, CA 15-3, OVX1, and macrophage colony-stimulating factor (M-CSF) has been explored in small-scale studies with promising results.<sup>35-37</sup> The combination of CA 125, TAG 72, and CA 15-3 has demonstrated a specificity of 99.9 percent.<sup>35</sup> Obviously, the use of several marker assays involves considerable laboratory effort, but improvements in specificity could ultimately lower the number of invasive procedures required to evaluate false-positive screening results.

#### MOLECULAR BIOMARKERS

In the last few years, there has been an expansion of the knowledge base concerning the molecular biology of ovarian cancer. Indeed, numerous molecular genetic lesions have been identified and

may be useful for screening detection of ovarian cancer (Table 5). As yet, the direct assay of a genetic lesion has not been applied clinically as a screening detection tool. The issue of targeting a particular gene or gene product for screening, however, is a complex topic and requires a thorough understanding of the molecular pathogenesis for the particular disease.

Most of the work in ovarian cancer has focused on mechanisms or genes involved in the regulation of cell proliferation (e.g., tumor suppressor genes and growth factors). The other critical steps in acquiring a malignant phenotype include local invasion, metastasis, and immunologic responses. In ovarian cancer it is unclear which of these mechanisms should be targeted for screening. Clearly, the first step in developing molecular markers for screening would be the elucidation of the mechanisms of early ovarian neoplasia. Because the normal ovary is not accessible for tissue sampling without performing an invasive procedure, the second step would be the development of technically feasible methods for the direct assay of genetic markers.

Of the currently known molecular

genetic lesions in ovarian cancer, mutations or deletions of the *p53* tumor suppressor gene are the most common and have been described in 50 percent or more of advanced-stage ovarian cancers. The *p53* gene appears to be involved in cell-cycle regulation, where loss of normal *p53* function through mutations or deletions can lead to deregulated cellular proliferation and transformation.<sup>38,39</sup> A correlation between *p53* mutation and prognosis in patients with ovarian cancer has not been demonstrated, although mutation and/or overexpression does correlate with advanced-stage disease.<sup>40</sup> Although *p53* gene mutations can be

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**About 95 percent of cases of ovarian cancer are sporadic in nature with no discernible pattern of inheritance.**

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identified by a variety of different laboratory techniques, the use of this gene for detection is limited because mutations are a relatively rare finding in possible precursor lesions such as cystic adenomas and LMP tumors.<sup>41</sup>

Abnormalities of several different classes of proto-oncogenes in ovarian carcinoma have also been described.<sup>42</sup> In addition to the *p53* gene, the most notable findings have been overexpression of *MYC* (30 percent), *EGFR* (35 percent), and *ERBB2* (24 percent). In the case of *EGFR* and *ERBB2*, overexpression of these genes may correlate with a poor prognosis in patients with advanced disease.<sup>43,44</sup> Unlike other common epithelial malignancies, such as lung and colon cancer, mutation and/or amplification of the *RAS* family of genes is relatively uncommon in ovarian cancer, except in the case of mucinous tumors of the ovary. This suggests that mucinous ovarian tumors may

be distinct in terms of pathogenesis from other epithelial ovarian tumors. Overexpression of M-CSF and its receptor, *FMS*, has also been reported,<sup>45</sup> although the number of reported cases is small.

The genetic complexity of ovarian cancer and the need for additional study are further emphasized by the demonstration of genetic losses from multiple chromosomes.<sup>46</sup> Several recent studies, however, have identified nonrandom deletions of genetic material from chromosomes 3, 6, 11, and 17 in ovarian carcinoma.<sup>47-55</sup> Indeed, with the identification of hereditary forms of ovarian cancer,<sup>56,57</sup> genetic studies of these families by linkage analysis can allow the identification of common genetic abnormalities.

One such abnormality has recently been localized to chromosome 17q and has been termed the *BRCA1* gene.<sup>58,59</sup> Although the exact nature of this gene is unknown, inheritance of a predisposition to breast and ovarian cancer in these families has a penetrance of up to 80 percent. This inherited gene, however, will probably only account for a small fraction of ovarian cancer cases. Further study of this gene will undoubtedly contribute to our understanding of the etiology of ovarian cancer and may lead to the development of other screening detection strategies for the general population.

### **Clinical Applications: Screening Detection Studies**

The recognition of a clinically detectable anatomic lesion and associated biologic phenomena has provided the basis for the design of screening detection studies. The major published studies have all used various ultrasound techniques and/or CA 125. There have been no randomized studies comparing the various screening strategies with clinical observation alone.

The value of CA 125 as a potential screening tool has been assessed in four separate studies. Zurawski et al reported the results of serum CA 125 testing in 105

**Table 5**  
**Molecular Markers in Ovarian Cancer**

Gene	Abnormality	Percent
p53	Overexpression/mutation	55
ERBB2	Amplification/overexpression	24
EGFR	Overexpression	35
RAS	Amplification, mutation	18
MYC	Amplification	30
FOS	Overexpression	100
FMS	Overexpression	83
TGFA	Overexpression	20

patients who developed ovarian cancer after having previously banked serum specimens in the JANUS serum bank in Norway.<sup>30</sup> In this study median CA 125 levels of the patients who developed ovarian cancer were significantly elevated over controls. Interestingly, the mean time between serum collection and the diagnosis of cancer was 68.2 months.

Helzlsouer et al reported a case-control study of 37 patients who had previously donated blood to a serum bank.<sup>60</sup> Using a cutoff CA 125 value of 35 U/mL, specificity for detection of ovarian cancer within three years of diagnosis was 100 percent, although sensitivity was only 57 percent.

Einhorn et al reported the results of initial screening with CA 125 in 5,550 subjects.<sup>61</sup> In this study 175 patients with initially elevated CA 125 values were selected for intensive clinical follow-up. A total of six ovarian cancers were subsequently diagnosed (two each for stage I, II, and III) in postmenopausal patients. Three ovarian cancers were also diagnosed in patients younger than 50 years, who were not selected for intensive follow-up (one stage I, two stage III). Using

a CA 125 cutoff value of 35 U/mL, the specificity for patients older than 50 years was 98.5 percent compared with 94.5 percent for patients 50 years or younger. This study confirms the limitations of screening younger patients where false-positive findings can be problematic.

Jacobs et al have also reported the use of CA 125 as a screening modality.<sup>62</sup> In this study of 22,000 patients older than 45 years, if an initial serum CA 125 was elevated, then ultrasonography was performed. If the ultrasonographic findings were abnormal, then surgery was performed. In total there were 340 abnormal CA 125 results and 41 abnormal ultrasound examinations followed by surgery. Eleven ovarian cancers were diagnosed (four stage I and seven stage III/IV). Specificity for CA 125 alone was 98 percent, but when combined, specificity for sequential CA 125 and ultrasonography was 99.9 percent with a positive predictive value of 26.8 percent.

These studies taken together suggest that (1) elevated CA 125 can be observed in advance of clinically detectable disease, (2) CA 125 screening is more specific in an older subset of patients, and (3)

CA 125 with ultrasound is superior to CA 125 alone as a screening modality. Unfortunately, the sensitivity of CA 125 in detecting ovarian cancer is difficult to assess in the larger studies, but probably is in the range of 50 to 70 percent. Because CA 125 is elevated in less than 50 percent of stage I ovarian cancers, the need for combined screening modalities becomes clear. Additionally, because many ovarian cancers diagnosed were either advanced stage or, in some cases, LMP tumors, the utility of screening can be questioned, because such diagnoses in population-based trials with a mortality endpoint would raise the issue of length and lead time bias.

Campbell et al published the first prospective study using ultrasound as the primary screening modality.<sup>17</sup> In 5,479

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***CA 125 has been the most extensively studied biomarker in ovarian cancer.***

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self-referred patients screened with abdominal ultrasonography, abnormal findings were surgically evaluated in 326 patients. A total of nine ovarian cancers were found; however, three tumors were LMP and four were cancers metastatic to the ovary. In fact, only two primary invasive ovarian cancers were found, both of which were early stage. Specificity in this study was 97.7 percent. A total of 36 surgical procedures were required to diagnosis each malignant ovary. Thus, abdominal ultrasonography alone has a specificity that approximates CA 125 as a single-screening modality.

Studies using TVS have demonstrated that this technique may be useful as a screening modality. DePriest et al have screened 3,220 patients using TVS and morphologic assessment of the ovary in

cases with abnormal sonographic findings.<sup>8</sup> In this study 44 abnormal scans were surgically evaluated, and three ovarian cancers were diagnosed (one stage I, one stage III, and one granulosa cell tumor). The overall specificity was 98.7 percent. Interestingly, all three patients with ovarian cancer had normal CA 125 determinations and normal pelvic examinations. Although not statistically significant, the incidence of benign serous cystadenomas in patients with a family history of ovarian cancer was twice the rate observed in patients without such a history. This observation suggests that cystic lesions of the ovary may in some cases be a pathologic precursor of ovarian cancer. This study also establishes the benefit of morphologic assessment of the ovary in screening studies.

One strategy to improve the effectiveness of ovarian cancer screening would be to target populations at increased risk for the development of the disease, such as those with a family history of ovarian cancer. Bourne et al reported the results of such a strategy in screening patients with TVS in combination with color flow Doppler imaging and morphologic assessment.<sup>63</sup> In screening 1,601 patients, 57 percent required repeat TVS to confirm the presence of the mass. Six ovarian cancers were diagnosed (two stage I, three LMP tumors, and one stage III). Karlan et al reported screening 597 patients with a family history of cancer with CA 125, TVS, and color flow Doppler imaging.<sup>64</sup> Initially, 115 patients had an abnormal TVS, and 68 had an abnormal CA 125. After repeat TVS or because of abnormal findings from color flow Doppler imaging, 19 patients underwent surgery. At the time of this report, one LMP tumor has been diagnosed. Similarly, Muto et al reported screening 386 patients with TVS and color flow Doppler imaging, with 36 patients undergoing surgery.<sup>65</sup> No ovarian cancers were reported. Although these studies use techniques that provide exceptionally de-

tailed pathologic descriptions of the ovary, the overall results in screening a targeted at-risk patient population are mixed. One may argue that an insufficient number of patients were studied; however, when considering only invasive stage I ovarian cancers, over 2,500 patients were screened resulting in 116 surgeries to diagnose two stage I cancers.

Another strategy to improve sensitivity and specificity in screening for ovarian cancer involves the use of multiple serum tumor markers. Because less than 50 percent of patients with stage I ovarian cancer will have an elevated CA 125, the addition of other markers in the screening strategy could potentially improve sensitivity. Woolas et al reported a retrospective study of CA 125, M-CSF, and OVX1 serum levels in 46 patients with

patients previously screened and found to have a CA 125 greater than 20 U/mL, specificity could be greatly improved by defining a positive test as an elevated CA 125 in combination with either an elevated CA 15-3 or TAG 72.3. Additionally, these investigators noted that in most patients an elevated initial CA 125 in the absence of malignant disease tended to normalize over time. The investigators suggest that specificity improvements may be achieved with multiple markers in conjunction with serial CA 125 determinations.

### Conclusions

Despite advances in the medical and surgical treatment of patients with ovarian cancer, early diagnosis is a relatively un-

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for the design of screening detection studies.*

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stage I ovarian cancer, 237 patients with benign masses, and 204 disease-free patients previously screened by CA 125.<sup>36</sup> In this study 98 percent of patients with stage I ovarian cancers had an elevation of at least one of the markers. The combination of the three assays was significantly better than CA 125 alone in predicting malignancy. The use of multiple markers can lower specificity, however, as highlighted by the finding that 11 percent of healthy patients also had an elevation of one of the markers.

Jacobs et al addressed the issue of specificity in a report using CA 125 in combination with CA 15-3 and TAG 72.3.<sup>35</sup> This combination of markers had previously been demonstrated to be useful in predicting malignancy in patients with adnexal masses. Using serum from

common event, and death from disease occurs in most women diagnosed with this malignancy. Because of these facts, efforts to reduce disease-related mortality are now focusing on the early detection of disease during its preclinical phase. Early detection thus would shift the diagnosis to a point in the disease process where curative-intent therapy is more effective. An additional important strategy in solving the problem of ovarian cancer would be development of methods to prevent the occurrence of the disease. Although not the focus of this review, prophylactic measures such as oophorectomy, use of oral contraceptive, and interruption of fallopian tubes have been suggested as means for reducing an individual's risk of developing ovarian cancer.<sup>13,66,67</sup>

Ovarian cancer is a disease for which the development of a screening detection strategy is appropriate. Despite a relatively low prevalence, the disease poses a substantial risk of death for those afflicted. Importantly, effective treatment exists for those patients diagnosed with early-stage disease. Although no clear consensus exists as to the pathogenesis of the disease or the premalignant pathologic entity, anatomic lesions and tumor markers can be identified and are associated with preclinical disease in many cases. Until more precise pathologic or genetic markers for ovarian cancer are described, cystic ovarian lesions and serum tumor markers are at present the best available means for early detection.

Of the various techniques available for imaging the pelvis as part of a screening detection strategy, TVS has been extensively studied and is probably superior

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***Early detection would shift the diagnosis of ovarian cancer to a point in the disease process where curative-intent therapy is more effective.***

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to abdominal ultrasonography. The addition of color flow Doppler imaging and morphologic assessment of the ovary adds important information to gray-scale sonography, although the effectiveness of these added techniques in screening detection has not been clearly demonstrated. The utility of serum CA 125 for screening has been demonstrated, but specificity issues necessitate the combination of CA 125 with other modalities. The use of multiple serum tumor markers and serial CA 125 determinations may improve sensitivity and specificity, but studies to date have been limited. The current available data support the combination of

CA 125 and TVS as the modalities best suited for further clinical study.

Several conclusions can be drawn from the published prospective screening trials. First, the identification of patients with stage I ovarian cancer prior to the onset of clinical signs or symptoms is possible using presently available technology. As suggested by Jacobs, the minimum specificity level necessary for any screening strategy should be 99.6 percent and should achieve a positive predictive value of at least 10 percent.<sup>35,62</sup> In this context the use of physical exam, CA 125, or ultrasound alone as screening tools lacks the necessary specificity for population-based screening.

Second, patients with a family history of breast and/or ovarian cancer are at increased risk for development of the disease and may warrant special attention. Based on this risk, a heightened level of clinical surveillance may be justified even though randomized data are not available to support such an approach.

Third, although the combination of various modalities for screening has improved sensitivity and specificity, the influence of selection, lead, and length bias can become limiting factors in larger-scale screening trials and makes interpretation of nonrandomized studies difficult. As such, until prospective, randomized trials are conducted, the use of presently available technology for the detection of early ovarian cancer remains investigational and is not recommended for routine clinical use.

The question remains as to where to proceed with screening detection for ovarian cancer. Although prospective trials have provided compelling data supporting the use of TVS and serum biomarkers for screening detection, the need for randomized trials has become apparent. Such a study has been undertaken by the National Institutes of Health as part of the Prostate, Lung, Colorectal, and Ovary study. In this randomized trial, patients between the ages of 60 and 74 years

will be assigned to receive an annual CA 125 and TVS versus a control group receiving routine medical care. This study should help answer the question as to the feasibility and value of screening detection using existing technology.

Additionally, research efforts need to be continued in several other areas. Improvements in diagnostic imaging technology, the refinement of screening study designs, and the development of novel markers of disease are needed.

Likewise, the prospective evaluation of new technology, possibly within the context of existing clinical trials, should be encouraged. Elucidation of the etiology and pathogenesis of ovarian cancer will further the effort of identification of more precise disease markers as well as treatment of patients with ovarian cancer. The identification of the *BRCA1* gene associated with hereditary forms of ovarian cancer will also provide a valuable insight into the etiology of this disease. **CA**

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