Screening for Ovarian Cancer

By Cindy Quinton Gladstone
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Ovarian cancer is the leading cause of gynecologic cancer mortality in North America. The disease has usually spread beyond the ovary by the time of diagnosis, and is associated with a five-year survival of 35% or less, as compared with 90% for Stage I tumours. To date, standard treatments have had little impact on mortality, and attention has focused on early detection through screening. A review of the evidence does not support such action. In fact, given the poor positive predictive value of pelvic examination, abdominal and transvaginal sonography, and/or serum CA 125 levels for ovarian cancer, as well as the potential harm of laparotomy, there is fair evidence to exclude such testing from periodic health assessments in asymptomatic pre- and post-menopausal women. The issue is less clearcut for high-risk women, with one or more first-degree relative(s) with ovarian cancer, or with one of the rare hereditary ovarian cancer syndromes. In such cases, the higher prevalence of disease may outweigh the risks of screening, although there is insufficient evidence to recommend for or against such a course of action. In all cases it would be prudent to examine the ovaries at the time of cervical cancer screening (see Chapter 73), as well as to refer women with a family history of ovarian cancer to an academic research center for follow-up.

Burden of Suffering

Ovarian cancer is the sixth most common female malignancy, after cancers of the breast, colon, lung, and uterus. The estimated incidence in Canada in 1993 was approximately 2100 new cases per year, about 4% of all new cancers in women.<sup>1</sup> Yet, because it is so lethal, it remains the leading cause of gynecologic cancer mortality in both Canada and the U.S.<sup>2</sup> Sparks suggests that for populations in which preventive measures have been applied for more common causes of death, the early detection of ovarian cancer “becomes the next focus of efforts to reduce premature death among women”.<sup>3</sup>

Familial instances account for 5% to 15% of all ovarian cancers.<sup>4,5</sup> A recent case-control study, conducted in Alberta, Canada<sup>6</sup> established a relative risk of 2.61 for individuals with relatives with ovarian cancer. (The 95% confidence interval for the ratio between the observed and expected number of malignancies in cases’ and controls’ relatives was 1.12-1.59, significantly different

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from 1). Public health records in the United Kingdom showed that, if two or more close relatives were affected, the lifetime risk to a sister or mother of a patient approached 40%. The rarer, hereditary cancer syndromes include: a) breast/ovary kindreds, b) Lynch II families, where both colonic and ovarian cancers occur, and c) site-specific cancers, involving only ovarian tumours. In addition to family history, other risk factors include advanced age, low parity, and nonuse of the oral contraceptive pill. At least one case-control report has shown a protective effect after as little as 3-6 months of oral contraceptive use.

Ninety percent to 95% of ovarian malignancies are classified as epithelial including serous, mucinous, endometrioid, clear cell, mixed epithelial, and undifferentiated histologies. Ten percent to 15% of these tumours are termed “borderline” or of “low malignant potential” because of their limited metastatic tendency and much higher 5-year survival rates. Tumour staging has been standardized by the International Federation of Gynecology and Obstetrics with Stage I tumours limited to the ovaries, Stage II including those with pelvic extension, Stage III involving those with peritoneal disease outside the pelvis and/or positive retroperitoneal or inguinal lymph nodes, and Stage IV comprising those with “distant” metastases.

At present, because of late and nonspecific symptomatology, and the relative inaccessibility of the ovaries to physical examination, only 25% of women with ovarian cancer have disease confined to the ovary at the time of diagnosis. While in recent studies the five-year survival rate for this group nears 90%, the comparable rate is 35% or worse for the majority of women, who have disseminated disease when diagnosed.

The natural history of ovarian cancer is not well understood. Rare case reports have suggested that malignancy may arise in benign cystadenomas. To date, however, no preinvasive lesion has been established. It may be that tumours arise de novo at multiple sites, as seen with primary peritoneal neoplasias. The problem of understaging due to inadequate surgery has hampered efforts to further define “typical” disease progression.

Maneuvers

Pelvic Examination

The sensitivity and specificity of the biannual examination have not been addressed. Patient size, body habitus, pelvic structure, and anxiety level would be expected to affect the accuracy of this maneuver, as would the expertise of the examiner, and the dimensions of the tumour itself. According to retrospective reports, chart reviews, and case series on this topic, pelvic examinations have missed from
10% to 100% of tumours diagnosed at laparotomy. A particularly high false positive rate would be expected in pre-menopausal women, given the increased prevalence of benign adnexal disease in this group.

One prospective comparison of preoperative ultrasound and pelvic examination in patients with pelvic masses yielded sensitivities (for detection of any pathology) of 83% and 67% respectively. Specificities were much higher at 94% and 96%.<sup>11</sup> The level of “blinding” of the examiners in this study, however, was questionable.

**Abdominal Ultrasound**

The literature in this area is limited once again to case series.<sup>12,13</sup> Campbell and colleagues<sup>14,15</sup> performed three annual screening scans on 5,479 self-referred, asymptomatic women over 45 years of age. Of 15,977 scans, 338 were positive. Almost 4% of subsequent laparotomies were negative. Five primary ovarian malignancies, all Stage I, were diagnosed, for a prevalence of 0.09%, a specificity of 97.7%, and a sensitivity of 100%. However, even with these test characteristics, the positive predictive value in this population was only 1.5%. Furthermore, there was no independent follow-up of the women with negative scans.

Clearly, despite the impressive sensitivity and specificity reported for abdominal ultrasonography, its ability to screen for ovarian cancer is limited by the low prevalence of such tumours in the general population.

**Transvaginal Sonography (TVS)**

This technique is said to be superior to abdominal ultrasonography, because the transducer is closer to the area of interest, permitting the use of higher frequency ultrasound and enhancing the image quality. There have been three recent case series reported by Van Nagell’s group<sup>2,16</sup> on screening for ovarian cancer using TVS. Specificity and sensitivity were calculated at 98.1% and 100% respectively. Other investigators have reported similar results.<sup>17</sup>

It has been postulated that transvaginal colour doppler may increase the specificity of TVS, because changes in tissue vascularity mediated by angiogenic tumour factors change impedance to bloodflow, even in Stage I cancers. One case series<sup>18</sup> supports this claim, with an abnormal colour doppler pattern seen in 0 of 30 normals, 1 of 10 benign masses, and 7 of 8 cancers.
CA 125

This tumour-associated antigen has been proposed for serologic screening for ovarian cancer. It is an antigenic determinant on a high molecular weight glycoprotein which is recognized by the monoclonal antibody OC 125.<sup>19</sup> Evidence concerning CA 125 screening is limited to 3 case-control studies, several case series,<sup>19-24</sup> and one “stochastic computer simulation”.<sup>25</sup>

When CA 125 levels were evaluated in healthy patients, patients with benign pelvic masses, and those with malignant masses (including ovarian carcinomas), a 93.3% sensitivity and 79.7% specificity were achieved, using the usual threshold of >35 U/ml.<sup>26</sup> As expected, using a higher cutoff increased specificity with a concomitant reduction in sensitivity.<sup>27</sup> False positives were seen with leiomyomas, inflammatory masses, endometriomas, and benign epithelial neoplasms. CA 125 is less sensitive in early stage disease, as well as in borderline and mucinous tumour types.

The most interesting study<sup>28</sup> involved a “blind” retrospective analysis of CA 125 levels using sera obtained from the JANUS serum bank, a Norwegian repository of specimens collected since 1973 from more than 100,000 individuals. CA 125 levels were measured for women who subsequently developed ovarian cancer and from matched controls. Based on these data, the authors quote a 30-35% sensitivity (for a threshold value of 35 U/ml) for CA 125 levels drawn 2 years prior to diagnosis. Specificity was 95.4%. Specificity could be further increased when the doubling of an initially elevated CA 125 value was used as the criterion for positivity.<sup>29</sup>

Combination Screening

When a combination of preoperative clinical examinations, abdominal ultrasonography, and CA 125 were performed in women with ovarian masses, results in post-menopausal women suggested much lower sensitivities, but higher specificities for all maneuvers than reported elsewhere. Test characteristics were poorer in pre-menopausal women. Using this multimodal approach the authors were able to increase the positive predictive value of screening to 100% in post-menopausal women. Clearly this reflects the high prevalence of disease in this pre-selected population (24% in the pre-menopausal women and 59% in the post-menopausal group).<sup>30</sup>

Another multimodal screening study<sup>31</sup> included only post-menopausal volunteers, who underwent a routine pelvic examination and CA 125 measurement (cutoff 30 U/ml), followed by ultrasonography if indicated. Only one case of ovarian cancer was detected. As anticipated, specificities were increased to 99-100% by the combination of two or three of the maneuvers.
A recent decision analysis, designed to estimate the effectiveness of an ovarian cancer screening with CA 125 levels and transvaginal sonography in a cohort of 40-year-old women, suggested that screening increased the average life expectancy in this population by less than one day.

Costs

There are no randomized controlled trials of screening for ovarian cancer. The potential costs of screening all women over 45 years of age are prohibitive. The cost in the U.S. to screen the 43 million eligible women of this age with an ultrasound U.S. ($275 each) and a CA 125 level U.S. ($45 each) has been estimated at over U.S. $13 billion yearly, with no guarantee of a reduced death rate.<5>

Treatment Efficacy

Surgery Alone

Two recent case series have reported results of a "watch and wait" approach, without adjuvant therapy, following initial surgery. In those patients with early stage tumours who had undergone the most extensive preoperative staging, 100% 5 year disease-free survival was achieved with surgery alone.<32> Prognosis for early stage tumours with capsular rupture or positive peritoneal washings was slightly worse.<33>

Chemotherapy

The literature on chemotherapy consists mostly of trials of single-agent or combination regimens in patients with advanced ovarian cancer. Trials in early-stage disease are plagued by inconsistencies of staging and grading. In one study, patients with early stage ovarian cancer were randomized to receive melphalan or no treatment. Five-year disease-free survival for the two groups was not statistically different (p>0.05) at 91% and 98% respectively.<34>

A companion study randomized women with poorly differentiated Stage I or II tumours to receive either melphalan, or a single dose of intraperitoneal Chromic Phosphate, a radioisotope. Five year disease-free survival was 80% for both groups. Overall survival for the two groups was approximately equal. The authors conclude that Chromic Phosphate is the preferred treatment, because of the risk of myelosuppression, gastrointestinal toxicity, and leukemias associated with Melphalan. Both Chromic Phosphate and Melphalan toxicity have been observed by other investigators.<35>
Radiotherapy

There is a scarcity of randomized controlled trials of radiotherapy. Dembo and colleagues<36> postoperatively randomized patients with Stage I tumours to “watchful waiting” or pelvic irradiation. Relapse rates depended more on the degree of differentiation of the tumours than on treatment received.

Adverse Effects

The unfavourable effects of screening, (including patient anxiety due to false positive results, and the false sense of security occasioned by false negative results) have remained largely unquantified. In those with a family history of ovarian malignancy, the side effects of prolonged hormonal replacement therapy following prophylactic oopherectomy must also be considered.

Buchsbaum<37> reported a startling rate of adverse outcomes of surgical staging of ovarian carcinomas, including 74 complications in 154 patients and one postoperative death. Most other authors have noted far fewer adverse outcomes of diagnostic laparotomy.<38-40>

Diagnostic laparoscopy may offer a less invasive, and presumably less risky, alternative to laparotomy. However, primary endoscopic surgery is not generally accepted for routine management of suspected ovarian cancer, because of the fear of spreading malignant cells. Guidelines for the pelviscopic management of ovarian masses are currently under review.

Familial Ovarian Cancer

Routine screening has been widely advocated in this population, in which the greater prevalence of disease should markedly increase the positive predictive value of all detection measures. In a screening study in asymptomatic women with at least one first degree relative with ovarian cancer, the prevalence of ovarian cancers was 3.9 per 1,000. This is much higher than the 0.4 per 1,000 prevalence quoted for the general population. The false positive rate was also higher, however, because of the higher incidence of benign ovarian masses. The positive predictive value of ultrasonography under these circumstances was considerably higher than usual, at 7.7%.<4>

Based on such evidence, many researchers advocate combination screening in an academic centre for all women with one or more first-degree relative(s) with ovarian cancer. As tumours tend to develop at a younger age in this group, it has been suggested that such screening begin at age 30. In addition to screening, prophylactic oopherectomy is recommended, particularly where there is a history of hereditary ovarian cancer. Unfortunately, even this radical prophylaxis does not
guarantee immunity from cancer, as rare case reports of postoperative disseminated intraabdominal carcinomatosis have been published.

Recommendations of Others

The U.S. Preventive Services Task Force concluded that screening of asymptomatic women for ovarian cancer is not recommended.\textsuperscript{41} This group does indicate that it is “prudent” to examine the adnexa, if a pelvic examination is to be done for other reasons.

For pre- and post-menopausal women without a family history of ovarian cancer, the American College of Physicians (ACP) does not recommend screening (ultrasound or CA 125). For women with a family with hereditary ovarian cancer syndrome, ACP recommends referral for specialist care. ACP also recommends that for other women with a family history of ovarian cancer (in one or more relatives), decisions about screening be made based on other risk factors (age, parity and history of oral contraceptive pill use).

Conclusions and Recommendations

There is fair evidence in published clinical research to exclude screening for ovarian cancer, either by abdominal examination, pelvic or transvaginal sonography, or CA 125 levels, from the periodic health examination of asymptomatic pre- and post-menopausal women (D Recommendation). It would be reasonable to examine the adnexa if a pelvic examination were being done for another reason, such as cervical inspection or pap smear.

There is insufficient evidence to recommend for or against screening in individuals with one or more first-degree relatives with ovarian cancer (C Recommendation). However, in light of the significantly higher incidence of ovarian malignancy in such women, expert opinion currently suggests that they be referred to an academic research centre for regular combination screening with pelvic examination, ultrasonography, and determination of CA 125 levels. There is little evidence concerning the frequency of such screening.

Unanswered Questions (Research Agenda)

Well-designed clinical trials are needed to elucidate further the natural history of ovarian cancer, and to assess multimodal screening for ovarian cancer, to determine whether the combination of pelvic examination, tumour markers, and transvaginal sonography will lead to reduced mortality. Further assessment of the test characteristics for these screening maneuvers in well-defined populations, such as those with a familial risk of ovarian cancer, would also be of value. The cost-
effectiveness of screening for ovarian cancer will depend on the
determination of its effectiveness, if any.

Evidence

Articles assessing screening for ovarian malignancy were
obtained by a computerized search (MEDLINE from 1975 onwards)
using the MESH headings screening, ovarian neoplasms, and one of
either ultrasonography, CA125 antigen, neoplasms-staging, surgery,
chemotherapy, or radiotherapy. Only references in English were
retrieved. Review articles, and those dealing with advanced stages of
ovarian cancer or nonepithelial tumours (see below) were excluded.
Content experts were consulted to ensure that all relevant research
was analyzed. A Technical Report (1992) including a full reference list is
available upon request. This review was initiated in January 1992 and

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### Screening for Ovarian Cancer

<table>
<thead>
<tr>
<th>Maneuver</th>
<th>Effectiveness</th>
<th>Level of Evidence</th>
<th>Recommendation</th>
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<tr>
<td><strong>For Asymptomatic Pre- and Post-Menopausal Women</strong>&lt;br&gt;Screening by pelvic exam, ultrasound, transvaginal sonography (TVS), serum tumour antigen (e.g CA 125) or combination</td>
<td>Poor positive predictive value for early detection of ovarian carcinoma. Effectiveness of screening unknown. Evidence of harm from diagnostic laparotomy. Few well-controlled studies on treatment; better prognosis with early stage cancers.</td>
<td>Case series&lt;2,11-24,30,31&gt; (III) and case-control studies (for CA 125 only) &lt;26-29&gt; (II-2)</td>
<td>Case series&lt;37-40&gt; (III) Randomized controlled trials&lt;34-36&gt; (I) and case series&lt;32,33&gt; (III) for various therapies</td>
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<tr>
<td><strong>For High-risk Women with &gt; 1 First-degree Relative with Ovarian Cancer</strong>&lt;br&gt;Multimodal screening (pelvic exam, TVS, CA 125)*</td>
<td>Evidence of higher positive predictive value for detection because of higher prevalence in this group. Effectiveness of screening unknown.</td>
<td>Case series&lt;4&gt; (III)</td>
<td>Insufficient evidence to recommend for or against screening (C)</td>
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* The frequency of screening recommended by experts in this area is twice yearly. There is little evidence to support this.