

American College of Radiology ACR Appropriateness Criteria®

Clinical Condition: Ovarian Cancer Screening

Variant 1: Premenopausal or postmenopausal female: low risk.

Radiologic Procedure	Rating	Comments	<u>RRL*</u>
US pelvis transabdominal	2		None
US pelvis transvaginal	2		None
US pelvis with Doppler	2	If there is blood flow with color, spectral waveform will quantify the flow.	None
CT pelvis with or without contrast	2		Med
MRI pelvis with or without contrast	2		None
<u>Rating Scale:</u> 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

Variant 2: Premenopausal female: high risk (personal history or family history).

Radiologic Procedure	Rating	Comments	<u>RRL*</u>
US pelvis transvaginal	7		None
US pelvis with Doppler	5	If there is blood flow with color, spectral waveform will quantify the flow.	None
US pelvis transabdominal	4		None
MRI pelvis with or without contrast	2		None
CT pelvis with or without contrast	2		Med
<u>Rating Scale:</u> 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

Variant 3: Postmenopausal female: high risk (personal history or family history or elevated CA 125).

Radiologic Procedure	Rating	Comments	<u>RRL*</u>
US pelvis transvaginal	8		None
US pelvis with Doppler	7	If there is blood flow with color, spectral waveform will quantify the flow.	None
US pelvis transabdominal	4		None
CT pelvis with or without contrast	2		Med
MRI pelvis with or without contrast	2		None
<u>Rating Scale:</u> 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

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OVARIAN CANCER SCREENING

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Summary of Literature Review

Ovarian cancer is the most frequent cause of death from gynecologic malignancy in the United States [1]. Approximately 22,200 new cases are diagnosed each year, and an estimated 16,210 of these women will die of their disease [2]. In the United States, one woman in 70 (1.4%) will develop ovarian cancer during her lifetime compared to one in eight for breast cancer. Symptoms usually do not become apparent until the tumor compresses or invades adjacent structures, ascites develops, or metastasis becomes clinically evident. As a result, 70% of women with ovarian cancer have advanced disease at diagnosis with a 5-year survival rate of 15%-20% compared to the 5-year survival rate of 90% in patients with stage I disease [1]. Because of the significant differences in survival rates between early and advanced cancers, a screening method for detecting early ovarian cancer has been sought. Clinical evidence suggests that the preclinical phase for ovarian cancer may be less than two years. This rapid growth pattern may imply difficulty in detecting early, resectable tumors.

Patients at risk include those of low parity, decreased fertility, and delayed childbearing. The annual incidence increases with age, from 20 per 100,000 in women age 30 to 50 years and 40 per 100,000 in women age 50 to 75 years. The strongest risk factor for ovarian cancer is familial evidence of ovarian cancer, reported in 7% of women with the disease. A patient with a history of familial ovarian cancer (two or more first-degree relatives—mother, sister, daughter) may have as much as a 50% chance of developing the disease. The presence of a hereditary ovarian cancer syndrome includes occurrence of ovarian, breast, and/or related cancers such as endometrial and gastrointestinal (Lynch II syndrome) in multiple members of two to four generations. These women present with the disease at an earlier age (45 to 52 compared to 59 years in the general population). The risk

of ovarian cancer is elevated among women who have a first-degree relative with breast cancer (1.5 times) or colorectal cancer (1.9 times). Another group of patients shown to be at elevated risk for ovarian cancer are those with BRCA 1 or BRCA 2 mutation. They have a 30% risk for developing ovarian cancer up to age 60 [3].

Women with a positive family history and a familial tendency for ovarian cancer should be counseled in their early 20s by a gynecologic oncologist or geneticist about their risk, with clinical follow-up in their 30s and possibly preventive surgery (ie, prophylactic oophorectomy). Patients in the reproductive age group may be counseled on the benefits of oral contraceptives. Studies have demonstrated a decrease in ovarian cancer risks (as high as 50%) in patients taking oral contraceptives, with the protective effect increasing with duration of use.

Current screening tests for detecting ovarian cancer include physical examination, tumor markers (eg, CA 125), and imaging methods such as transabdominal ultrasound (TAS) and transvaginal ultrasound (TVS) with color Doppler and power Doppler, computed tomography (CT), and magnetic resonance imaging (MRI). The pelvic examination, which can detect a variety of gynecological disorders, is not sensitive or specific for detecting ovarian cancer. In general, ovarian malignancies have disseminated by the time they are palpable.

Tumor Markers

CA 125 is the antigenic determinant of a glycoprotein expressed by epithelial ovarian tumors and other tissues of müllerian origin [4]. It is elevated (>35 U/ml) in more than 80% of patients with epithelial ovarian cancer; however, it is only 25% sensitive for early disease [1]. It is not specific for ovarian cancers since it can be elevated in other malignant conditions (pancreatic, endocervical, and fallopian tube cancers) and in benign conditions such as pregnancy, endometriosis, leiomyomas, pelvic inflammatory disease, hepatitis, and cirrhosis. CA 125 fluctuates during the menstrual cycle, and in premenopausal women, more than 90% of CA 125 elevations are falsely positive for ovarian carcinoma. Therefore, alone it does not have a sufficiently high sensitivity to be recommended for routine ovarian cancer screening. However, CA 125 levels exceeding 65 U/ml are predictive of malignancy in 75% of postmenopausal women with pelvic masses. The primary usefulness of CA 125 is in the management of patients with documented ovarian cancer. Other tumor markers such as NB/70K, a marker for epithelial mucinous adenocarcinomas of the ovary, may increase the sensitivity of the CA 125 marker when used concurrently.

Recently, two types of serum biomarker assay screening techniques have been reported to have high accuracy in

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detecting ovarian cancer, even in its earliest stages. Serum proteomics assay, which uses mass spectroscopy of serum proteins and gene products, has shown a sensitivity of 100%, specificity of 99%, and positive predictive value (PPV) of 94% [5]. This test has limited availability, and is currently investigational, but has significant potential as a serum screen for ovarian cancer, including its earliest stages. Another serum screen that is being evaluated is a multiple analyte panel (Yale Early Detection Assay [YEDA] test) that includes leptin, prolactin, osteopontin, macrophage inhibiting factor, CA 125, and insulin-like growth factor [6]. The assessment of four analytes resulted in a sensitivity of 95%, specificity of 95%, PPV of 95%, and negative predictive value of 94%. Clinical trials that include serum screening combined with imaging (TVS and MRI) have been proposed and are currently underway.

Ultrasound

Multiple studies have suggested that US is an accurate imaging method for distinguishing normal from abnormal ovaries, especially in the postmenopausal female. The first large study to examine the use of TAS for detecting ovarian cancer was reported by Campbell et al [7]. In this study, premenopausal and postmenopausal women had three annual TAS examinations. A total of 338 had abnormal screening, five primary ovarian cancers and four metastatic ovarian cancers were detected, for an overall specificity of 97.7%. Two of the primary cancers were found at the first screening and three a year after the first screening. One in 50 women with abnormal TAS had ovarian cancer, which means that of 50 laparotomies, one case of primary ovarian cancer would be found, with no cancer present in the other 49. The study demonstrated the usefulness of TAS for detecting ovarian abnormalities, particularly in postmenopausal women, and its lack of specificity due to its suboptimal resolution of the morphological features [7]. Jacobs et al [8] screened 22,000 asymptomatic postmenopausal women with a combination of both CA 125 tests and TAS. Their screening program had a specificity of 99.9% with sensitivity of 78.6% at one year and 57.9% at 2-year follow-up. This was the first study to show a positive effect of screening, with the length of survival of screened patients, averaging 72.9 months versus 41.9 months in the control group.

By placing a high-frequency transducer closer to the adnexa, TVS increases resolution and improves the ability to detect abnormalities of the ovary. In a study of postmenopausal females, Fleischer et al [9] found that TVS was able to identify both ovaries in 60% of the cases and at least one ovary in 81% of the cases. Most of the ovaries not visualized were atrophic. These data suggest that not visualizing the postmenopausal ovary with TVS confirms lack of an abnormality. TVS has demonstrated that 17% of postmenopausal ovaries contain simple cysts

that are transient and frequently benign. The prevalence of these adnexal cysts or cyst activity is independent of hormone replacement therapy.

The efficacy of screening for ovarian cancer using TVS continues to be investigated in several large population studies [10]. In 2000, the University of Kentucky study reported data on 14,469 asymptomatic women. Out of this population, 180 studies were abnormal, with 17 diagnosed with ovarian cancer (11 with stage I, 3 with stage II, 3 with stage III, and 4 with “interval cancers”). Their sensitivity was 81% and specificity 98.9%. The use of TVS was associated with decreased stage of ovarian cancer at detection and decreased mortality [11]. In a large screening study from Japan on 183,034 women, 22 primary ovarian tumors and two metastatic lesions were found, for a detection rate of 0.04%. Of the 22 primary ovarian cancers found, 17 (77.3%) were stage I; markers were positive in five (29.5%). The percentage of stage I ovarian cancers increased from 29.7% to 58.8% with TVS screening, with 77.3% of primary ovarian cancer found in stage I [12].

In the U.S., a recent report of the PLCO (prostate, lung, colorectal, and ovarian) cancer screening trial including 39,115 women found abnormal TVS in 4.7% and an abnormal CA 125 level in 1.4% [13]. Twenty-nine ovarian cancers were identified (26 ovarian, two fallopian tube, one peritoneal) nine had low malignant potential, and 20 were invasive. PPV was 3.7% for abnormal TVS, 1.0% for abnormal CA 125, and 23.5% when both were abnormal. The effect of screening on mortality will require additional accrual of patients, which may take 5-10 more years.

One of the factors limiting the efficacy of screening is the small percentage (approximately 10%) of ovarian cancers that have genetically identifiable risk factors.

In an attempt to improve the specificity, Bourne et al [14] evaluated women with positive family history (one first-degree or second-degree relative) of ovarian cancer with TVS. Three primary stage I ovarian cancers were found, consistent with a false positive rate of 5.5% and a PPV of 7.7%.

Karlan and Platt [15] found that 32 surgeries were performed to diagnose ovarian cancer in the low-risk population, compared to 17 surgeries in the high-risk population. In addition, they reported their experiences with 1,261 women screened; three resulted in detection of stage I ovarian cancers and seven in detection of the peritoneal variety [16].

Combining TVS with color flow Doppler (TV-CDS) imaging technique has been shown by many authors to further enhance the detection of early-stage ovarian cancer [17]. This is due to the unique characteristics of tumor neovascularity, which include vessel clustering,

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morphologically abnormal tumor vessels that contain areas of stenosis and dilation, and numerous arteriovenous malformations. Some of these characteristics have been observed using 3D US and/or contrast US [18-20]. A few studies have shown the potential for distinguishing the contrast kinetics with tumors having quicker uptake and longer dwell time [19-21].

Due to its expense and the technical expertise required for TV-CDS, it is probably best used in women with morphologically suspicious masses or those at great risk. In a high-risk population, Weiner et al [22] found TVS to have a specificity of 97.5% and PPV of 25% in detecting ovarian tumors, compared to a specificity of 99.9% and PPV of 60% for color flow imaging. The pulsatility or resistive index (PI or RI) value indicates decrease in resistance to blood flow in the distal vasculature and has been identified in malignant lesions as well as vascular benign masses. The neovascularity identified in malignant masses can also be seen in the formation of the corpus luteum. Therefore, to avoid unnecessary surgery, screening for premenopausal women should be done during days 1 to 12 of the menstrual cycle.

In postmenopausal women, low-resistance blood vessels are not seen within normal ovaries and when present are considered abnormal. The absence of intraluminal flow or high impedance flow in an ovary can potentially exclude malignancy [22]. However, morphologic characteristics remain the most important criteria in differentiating a normal from an abnormal ovary [23]. A large multicenter trial in Europe [24] also confirmed the accuracy of evaluating ovarian masses by their morphology. In particular, irregularly thickened walls and/or papillary excrescences are sonographic signs of potentially malignant lesions [24]. However, the use of TVS alone for detecting ovarian cancer has been shown to be of limited value [25].

Computed Tomography

Pelvic CT is not indicated for screening due to its inability to image small lesions, poor soft-tissue discrimination in the pelvis, high cost, and need for contrast material. The cost of MRI, in addition to the lack of resolution in the pelvis, precludes its use in screening for small ovarian abnormalities.

Ultrasound and CA 125 Testing Combined

In 1996, the cost of an US screening program prompted by an abnormal CA 125 level was estimated to be six times greater in the general population compared to patients with family history. The cost of screening for ovarian cancer is at least 10 times that of screening for breast cancer [26]. Of every 10,000 women participating in an annual screening program with CA 125 testing for 3 years, 800 would have an US scan because of an elevated CA 125 level, 30 would undergo surgery because of an abnormal US, and six would have ovarian cancer detected

at surgery (three will be diagnosed at early-stage disease and have a chance of a cure) [27].

In postmenopausal women, surgical evaluation may be recommended when the ovarian volume is enlarged (>8 cc) with an elevated CA 125 level or a normal CA 125 level with abnormal morphologic characteristics of the ovary (ie, complex or solid mass). If an ovarian simple cyst measures >5 cm in diameter or <5 cm with an elevated CA 125 level and abnormal morphology (such as focally thickened wall, papillary excrescence [24], or abnormal vascularity), surgical intervention may be considered.

The combined use of CA 125 testing and TVS as a secondary test in 6,532 screened women resulted in a specificity of 99.8% and PPV of 19%. The efficacy of this screening strategy continues in the investigation of United Kingdom Collaborative Trial of Ovarian Cancer Screening and in the United States in both the Cancer Genetics Network and the Gynecology Oncology Group Trials of High Risk Women. Outcome data on 95,000 women from the U.K. trial are anticipated by 2011 [28].

Summary

There is currently no sufficiently accurate screening test for ovarian cancer in women at average risk. This is undoubtedly related to the low prevalence of the disease in the general population and the lack of data from long-term outcome studies. Given the likelihood that ovarian cancer grows rapidly, an inexpensive and accurate screening test with high sensitivity that can be administered frequently as a screening study is needed. Without this and long-term data from large population trials, routine screening for ovarian cancer cannot currently be recommended. The results from large clinical trials comparing long-term mortality from ovarian cancer between screened and nonscreened cohorts are needed. The efficacy of screening for ovarian cancer with promising new techniques is under investigation. Future developments in serum screening with multiple analytes or proteomics may offer opportunities for identifying novel biomarkers or patterns of markers that will have a greater sensitivity and shorten the lead time for detecting preclinical disease [29,30].

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Additional information regarding radiation dose assessment for imaging examinations can

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be found in the ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#) document.

Relative Radiation Level Designations	
Relative Radiation Level	Effective Dose Estimate Range
None	0
Minimal	< 0.1 mSv
Low	0.1-1 mSv
Medium	1-10 mSv
High	10-100 mSv

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