American College of Radiology
ACR Appropriateness Criteria®

Clinical Condition: **Ovarian Cancer Screening**

Variant 1: **Premenopausal or postmenopausal female: average risk.**

Radiologic Procedure	Rating	Comments	RRL*
MRI pelvis without and with contrast	2		O
US pelvis transvaginal with or without Doppler	2		O
US pelvis transabdominal with or without Doppler	1		O
CT abdomen and pelvis without contrast	1		☢☢☢☢
CT abdomen and pelvis with contrast	1		☢☢☢☢
CT abdomen and pelvis without and with contrast	1		☢☢☢☢
MRI pelvis without contrast	1		O
FDG-PET/CT whole body	1		☢☢☢☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Variant 2: **Premenopausal or postmenopausal female: high risk (includes personal history or family history or known or suspected genetic predisposition or elevated CA-125).**

Radiologic Procedure	Rating	Comments	RRL*
US pelvis transvaginal with or without Doppler	6		O
US pelvis transabdominal with or without Doppler	4		O
MRI pelvis without and with contrast	2		O
CT abdomen and pelvis without contrast	1		☢☢☢☢
CT abdomen and pelvis with contrast	1		☢☢☢☢
CT abdomen and pelvis without and with contrast	1		☢☢☢☢
MRI pelvis without contrast	1		O
FDG-PET/CT whole body	1		☢☢☢☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

OVARIAN CANCER SCREENING

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Summary of Literature Review

Introduction/Background

There has been much debate about the role of imaging in ovarian cancer screening based on currently available evidence [1]. Ovarian cancer is frequently fatal, commonly discovered only after its widespread dissemination. Based on National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) registry data, metastatic disease is present in 63% of cases at the time of diagnosis and is associated with a low 5-year relative survival rate of 27% [2]. Only 15% of women have organ-confined disease at the time of detection [2]. These women have a substantially higher 5-year relative survival rate (92%) [2], suggesting that screening could be of benefit if aggressive cancers can be reliably detected at earlier stages. To evaluate current evidence on this topic, we considered: 1) the burden of ovarian cancer and salient risk factors; 2) new knowledge of its natural history; 3) prerequisites for effective screening tools; and 4) published clinical trial and observational data. We found no clear evidence to support screening women of average risk (no personal history, no family history, no known or suspected genetic predisposition, and no elevated CA-125). However, we provide an update on areas of investigation that may support a future role for imaging and serum biomarkers in special cases.

Epidemiology and Risk Factors

Ovarian cancer has a low associated disease prevalence, but a high mortality rate [2]. Among U.S. women, it ranks as the 9th most common cause of new cancer diagnoses, and the 5th most common cause of cancer deaths – it is projected to have accounted for 21,990 new cancer diagnoses and 15,460 cancer deaths in 2011 [3]. Primary risk factors include: presence of *BRCA1* or *BRCA2* mutations; strong family history (eg, 1st degree relative, particularly if premenopausal at the time of diagnosis); nulliparity, lack of breastfeeding, and lack of hormonal contraception use; and postmenopausal status [4]. Among all risk factors, a genetic predisposition is associated with the highest increase in cancer risk. A recent meta-analysis projected that 20-year-old *BRCA1* and *BRCA2* mutation carriers have 39% and 16% mean cumulative risks of developing ovarian cancer, respectively, by age 70 [5].

Natural History

Cancers that clinically fall under the umbrella of ovarian cancer are now known to have heterogeneous natural histories and tissue origins [6-10]. Five primary subtypes describe most epithelial ovarian cancers: serous, mucinous, clear cell, endometrioid, and transitional cell [9,10]. Serous cancers represent the majority of all ovarian cancers, are commonly diagnosed at late stages, and account for most ovarian cancer deaths [6-10]. Importantly, low-grade and high-grade serous tumors do not define a spectrum, but instead reflect distinct tumor biologies. Current evidence suggests that some benign serous cystadenomas may progress to low-grade serous cancers (the less common of the two) in an adenoma-carcinoma sequence [9]. High-grade serous cancers are thought to arise directly from surface epithelium [9]. They commonly demonstrate TP53 mutations and are also

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associated with *BRCA1* and *BRCA2* mutations [8,9]. Many high-grade "ovarian" serous cancers are now thought to be extraovarian in origin, arising instead from the distal fallopian tubes (fimbria), as initially suggested by histologic evaluation of specimens from *BRCA* mutation carriers who have undergone prophylactic salpingo-oophrectomy [6,8,9,11].

By mathematically modeling the behavior of ovarian cancers in hypothetical populations of *BRCA* mutation carriers and average-risk patients, researchers have gained insight into their natural history and have investigated a potential role for screening [6,7]. Based on their findings, current screening tools are expected to have low effectiveness because of the tendency for small cancers to spread rapidly [6,7]. Brown and Palmer [6], when modeling serous cancers in high-risk patients, projected that an annual screening tool for ovarian cancer would need to detect tumors as small as 0.5 cm in diameter in order to achieve a 50% mortality reduction.

Prerequisites for an Effective Screening Test for Ovarian Cancer

Test Performance Characteristics

Positive predictive value (PPV), defined as the number of true-positive cases divided by the total number of test-positive cases, is a critically important metric to consider in the context of ovarian cancer screening. Unlike the sensitivity and specificity of a diagnostic test, PPV incorporates both test performance and disease prevalence. A minimum PPV of 10% has been suggested as necessary for an ovarian cancer screening tool [4,12]. This implies that at least one cancer should be diagnosed in every 10 patients who undergo salpingo-oophrectomy for suspicion of malignancy. Given the low prevalence of ovarian cancer, very high specificity is needed for a successful screening tool. At an assumed prevalence of one case per 2,500 postmenopausal women per year, a test with perfect sensitivity (100%) would require a specificity of 99.6% to achieve a 10% PPV, and a test with 50% sensitivity would require an even higher specificity of 99.8% [4,12-14].

Mortality Reduction

Mortality reduction is also essential to substantiate ovarian cancer screening, and it should be demonstrated in randomized controlled trials to avoid biases typical of single-arm or other observational studies. Importantly, accomplishing a shift in stage distribution (eg, demonstrating that cancers of an earlier stage can be detected if screening is introduced), is necessary but not adequate to demonstrate the effectiveness of screening. This is because screening may simply detect a greater proportion of early-stage cancers that are indolent, thereby accomplishing a stage shift that does not meaningfully affect survival.

Salient Published Evidence

Most of the peer-reviewed imaging literature to date has dealt with pelvic ultrasound (US). Other cross-sectional imaging methods, including magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), and PET/CT, have no known or foreseeable role in screening. Attention has also been directed to the role of CA-125 (a widely known serum tumor biomarker) for screening, either alone or in combination with imaging (eg, US and CA-125).

Pilot United Kingdom Trial

In 1999, Jacobs et al [15] published a pilot randomized controlled trial in which postmenopausal women were randomized to a control group (n=10,977) or to annual screening with CA-125 (n=10,958) for 3 years. Patients with elevated CA-125 were referred to US, which was initially done transabdominally and then transvaginally when this approach became more widely available. At US, ovaries ≥8.8 mL were designated as abnormal, whereas ovaries with normal volume but abnormal morphology were considered equivocal and followed with subsequent US. Women with elevated CA-125 and abnormal US were referred for surgical consideration. An 86% compliance rate with at least one screen was achieved, establishing screening feasibility. PPV was reported to be 21%, suggesting the potential viability of a multimodal screening method. This trial substantiated resources for subsequent, larger randomized controlled trials.

Shizuoka District (Japan) Trial

In 2008, Kobayashi et al [16] published a randomized controlled trial in which postmenopausal women were randomized to a control group (n=40,799) or to five screening rounds of CA-125 and US (n=41,688). US was predominantly performed using a transvaginal approach. At US, ovaries were considered suspicious for malignancy if ovarian size was >4 cm and a complex morphology was apparent. In the screening group, further management ranged from annual follow-up to surgical intervention, depending on combined test results. Salient trial findings were twofold. First, ovarian cancer prevalence was lower (0.31/1,000) than in an expected United States population. Second, a statistically significant shift in stage distribution was not achieved.

United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) – Prevalence Screen

In 2009, Menon et al [17] published results of the first screen from the UKCTOCS, a randomized controlled trial in which postmenopausal women were randomized to a control group (n=101,359); multimodal screening (eg, annual CA-125 with transvaginal US as a follow-up test) (n=50,640); or annual transvaginal US alone (n=50,639). US results were considered abnormal if ovaries demonstrated a complex morphology or had simple cysts >60 mL, or if ascites was present [17]. Rather than using standard single cutoffs for CA-125 positivity, CA-125 results were designated based on the "risk of ovarian cancer algorithm," described by Menon et al [18] in earlier work. This algorithm incorporates patient age and CA-125 trends to triage further management, and is expected to improve CA-125 test performance, particularly its PPV and specificity [18]. In the prevalence screen, Menon et al [17] found that the multimodal strategy was superior to US alone, resulting in sensitivity, specificity, and PPV values of 89.4% , 99.8%, and 43.3% compared to 84.9%, 98.2%, and 5.3%, respectively. Whether these test performance characteristics can influence stage distribution or cancer-specific mortality remains to be seen, and will be determined when final study outcomes are reported.

United States Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial

In 2011, Buys et al [19] of the PLCO project team published results of the largest completed randomized controlled trial to date, in which postmenopausal women were randomized to a control group (n=39,111) or annual screening (n=39,105) with CA-125 for 6 years and transvaginal US for 4 years. US results were considered abnormal if ovarian or ovarian cyst volume was >10 mL, or if intraovarian lesions harbored projections into cysts or mixed solid and cystic components [19]. In 2009, Partridge et al [20] published results of the first four screening rounds, demonstrating low PPV (range: 1%-1.3%) and a predominance of late-stage cancers detected. In the final analysis, Buys et al [19] found no significant shift in stage distribution and no statistically significant reduction in cancer-specific mortality. False-positive results occurred in 3,285 women. Among this group, 1,080 (33%) underwent surgery for oophorectomy, 163 (15%) of whom had a major resulting complication [19]. Importantly, this study was powered to detect a 35% mortality reduction – smaller reductions could not be reliably resolved. However, based on projections of uncertainty, at most an 18% relative mortality benefit of screening was considered possible [19].

University of Kentucky Ovarian Cancer Screening Project

In 2007, van Nagell et al [21] published results of a single-arm screening trial conducted at the University of Kentucky. The patient population was mixed in menopausal status and level of risk, including both postmenopausal women and premenopausal women with a family history of ovarian cancer. While the results of this study indicated a potential shift in stage distribution and mortality reduction, the study design (with no control group and with a mixed-risk population) was subject to known epidemiologic biases [21]. As indicated above, PLCO randomized controlled trial results reported subsequently did not reproduce the findings of this single-arm study [19].

Biomarkers

In addition to CA-125, many serum biomarkers have been investigated as possible screening agents [22-29]. For example, in one of the largest and most recent studies to date, Cramer et al [23] conducted a two-tiered analysis of a spectrum of candidate biomarkers. Promising biomarkers were first tested in "phase II" specimens (from symptomatic patients with known ovarian cancer). A subset was then tested in "phase III" specimens from the PLCO screening trial (from asymptomatic patients prior to cancer diagnosis). The highest performing biomarkers in phase II specimens were CA-125, HE-4, transthyretin, CA-15.3, and CA-72.4. When tested in phase III specimens, performance was retained for most of them up to 6 months prior to diagnosis, but decreased at earlier timepoints. CA-125 was the best performing biomarker. In general, there is increased interest in (1) further optimization of CA-125 as a biomarker [18,30] and (2) additional serum biomarker investigation for early-stage ovarian cancer detection, particularly with a proteomic screening approach [22-27,29]. However, with the exception of CA-125, there is currently insufficient evidence available for determining the value of biomarkers in population-level ovarian cancer screening.

High-Risk Populations – *BRCA1* and *BRCA2* Mutation Carriers and Patients with a Strong Family History

To our knowledge, randomized controlled trials analogous to those in average-risk populations have not been conducted in high-risk populations. Several observational studies have been reported, all relatively small in sample size [31-35]. None concluded that ovarian cancer screening with CA-125 and/or US was a promising approach. Despite higher reported PPV in some studies (expected with higher disease prevalence), aggressive serous cancers — frequently seen in high-risk patients — were typically detected at advanced stages despite

screening [31-35]. Further insights into the role of screening in high-risk patients will be gained from the UK Familial Ovarian Cancer Screening Study (UK FOCSS) (available at: http://www.instituteforwomenshealth.ucl.ac.uk/academic_research/gynaecologicalcancer/gcrc/ukfocss/), a large, prospective single-arm screening study for women with a strong family history or genetic risk. More than 5,000 women were to be screened with CA-125 (using the risk of ovarian cancer algorithm [18]) and transvaginal US. UK FOCSS has completed recruitment and final study results are awaited.

Rebbeck et al [36] in a meta-analysis of studies published between 2002 and 2008, computed an 80% reduction in ovarian or fallopian tube cancer risk among high-risk patients who underwent prophylactic bilateral salpingo-oophrectomy. While studies used to perform this analysis are subject to known epidemiologic biases [37], prophylactic surgery remains recognized as the only effective means of risk reduction in high-risk patients [36]. Women with known or suspected genetic risk factors for ovarian cancer should be strongly advised to seek genetic counseling [13]. Moreover, given the success of prophylactic surgery in this setting, the American College of Obstetrics and Gynecology recommends that bilateral salpingo-oophrectomy be offered to all women with *BRCA1* or *BRCA2* mutations by 40 years of age [13].

Summary

- Ovarian cancer screening is not recommended in average-risk populations. Current randomized controlled trial results do not indicate a favorable shift in ovarian cancer stage distribution or in cancer-specific mortality reduction [19]. Results from the largest ovarian cancer screening study to date — the UKCTOCS — are awaited and should provide additional information regarding the effectiveness of screening in average-risk patients.
- Women with a known or probable genetic predisposition for ovarian cancer should be counseled that even in high-risk settings there is no evidence to support the effectiveness of ovarian cancer screening. Women at high risk should be advised to seek genetic counseling. Prophylactic salpingo-oophrectomy can substantially reduce ovarian cancer risks, and it should be offered to patients who are *BRCA1* and *BRCA2* mutation carriers [36].
- Primary challenges for ovarian cancer screening tools are twofold. First, the failure to achieve a clear shift in stage distribution in screening studies to date [16,19] suggests that the window between cancer development and dissemination is short, limiting the opportunity for early-stage detection. Second, very high specificity is required to reasonably avoid unnecessary surgeries and complications at the population level. These challenges make current imaging techniques poor candidate "stand-alone" screening tools. Future serum biomarker approaches, with or without concurrent pelvic US, are more likely to overcome these challenges. Such approaches are under active investigation and merit further research investment, particularly in high-risk patients.

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. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared to those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® Radiation Dose Assessment Introduction document.

Relative Radiation Level Designations		
Relative Radiation Level*	**Adult Effective Dose Estimate Range**	**Pediatric Effective Dose Estimate Range**
O	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢ ☢	0.1-1 mSv	0.03-0.3 mSv
☢ ☢ ☢	1-10 mSv	0.3-3 mSv
☢ ☢ ☢ ☢	10-30 mSv	3-10 mSv
☢ ☢ ☢ ☢ ☢	30-100 mSv	10-30 mSv
*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies".		

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Procedure Information
- Evidence Table

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.