Imaging and Screening of Ovarian Cancer

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KEYWORDS

• Ovarian cancer • Cancer screening • Randomized trials • Transvaginal ultrasound

KEY POINTS

- Ovarian cancer screening has not been shown to decrease mortality in average-risk women and is not recommended by any North American professional society.
- Randomized trials of ovarian cancer screening have not been conducted in women at high risk for ovarian cancer. Women with BRCA mutation or a family history of ovarian cancer are considered at high risk.
- Some professional societies recommend consideration of screening women at high risk using annual transvaginal ultrasound and serum CA-125; however, there is no evidence of mortality benefit.
- Prophylactic bilateral salpingo-oophorectomy in high-risk women is the only intervention that has been proven to decrease ovarian cancer mortality.
- Currently, the role of imaging in ovarian cancer screening is for confirmation of a clinically suspected diagnosis; more importantly, imaging is used for definitive characterization of incidental benign adnexal lesions in order to decrease rates of surgical diagnosis.

INTRODUCTION

Epithelial ovarian cancer is a malignancy with low prevalence and high mortality: although only 1.3% of women will be diagnosed with ovarian cancer during their lifetime,[1] ovarian cancer is the leading cause of gynecologic malignancy in the United States with 14,080 deaths due to ovarian cancer projected for 2017.[2] The high mortality of ovarian cancer is attributed to the presence of distant metastases at the time of diagnosis. Although localized ovarian cancer has a good prognosis with 5-year survival estimates of 92%, more than half (60%) of ovarian cancers are metastatic at time of diagnosis, which confers a much lower 5-year survival estimate of 29%.[2] This observation has fueled the effort to identify a diagnostic test that could be used to screen for ovarian cancer, in hopes of detecting disease at earlier stages when it is most treatable.

To date, ovarian cancer screening has not proven effective, due in part to its relatively low incidence rate, its pathophysiology, and the diagnostic test performance of currently available screening tools. The authors review what is known about the natural history of high-grade epithelial ovarian cancer, the results of the largest trials of ovarian cancer screening using transvaginal ultrasound (TVUS), as well as the current and future use of imaging in

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ovarian cancer detection. They also summarize the current consensus recommendations for women at average and high risk for ovarian cancer.

PATHOPHYSIOLOGY OF OVARIAN CANCER

Although the natural history of the development and spread of ovarian cancer is not fully understood, it is clear that tumors classified as ovarian make up a heterogeneous group of diseases. More than 95% of ovarian cancers are epithelial in origin, with the remaining 5% comprising germ cell and sex cord-stromal tumors.[3] Of the epithelial tumors, serous tumors are most common, representing 40% of all epithelial tumors.[3] A 2-phenotype classification of serous carcinomas has been proposed that distinguishes between low- and high-grade serous tumors, which are thought to represent distinct diseases with markedly different biological behaviors.[3] Low-grade serous lesions may arise from precursor lesions and are associated with several mutations including B-raf proto-oncogene serine/threonine-protein kinase (BRAF) and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS).[3] Their rate of growth is more indolent, and thus, they are also more likely to be detected at early stage by screening (**Fig. 1**). In contrast, high-grade serous tumors are associated with tumor protein 53 mutations and progress rapidly, making early screen-detection difficult (**Fig. 2**).[3] Examination of specimens from prophylactic bilateral salpingo-oophorectomy (PBSO) in BRCA1/BRCA2 mutation carriers has suggested that high-grade serous tumors may actually arise from the fallopian tubes rather than the ovary.[4,5]

Models of the natural history and progression of ovarian cancer have been used to estimate the sojourn time of clinically occult ovarian cancer. Based on pooled data from studies of serous cancers discovered at PBSO, Brown and Palmer[6] estimated that ovarian cancers spend approximately 4 years as in situ, stage I and stage II tumors, during which time they are typically too small to visualize even on gross examination of the ovaries and fallopian tubes. At time of progression to stage III/IV, median diameter is approximately 3 cm. Based on these findings, the investigators estimate that a screening test would need to detect tumors less than 4 mm in diameter to achieve 80% sensitivity; to reduce cancer mortality by 50% would require detection of tumors 5 mm in size.[6] Moreover, the known discrepancy in the biologic behavior of low- and high-grade serous tumors may limit the effectiveness of current methods available for screening. Results from one Markov model of serous ovarian cancers incorporating this 2-phenotype model suggest that application of currently available screening technologies would only result in modest (6.4%–10.9%) reductions in ovarian cancer mortality. This potential limitation is further supported by the high rate of interval cancers seen in screening trials of women with BRCA mutations.[7]

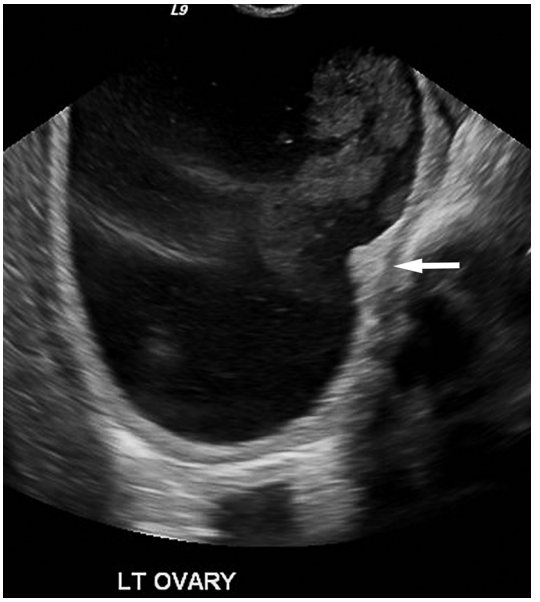

Fig. 1. Low-grade epithelial ovarian cancer. TVUS image of a 24-year-old woman presenting with symptoms of bloating and constipation shows a 12-cm complex left adnexal cyst with mural nodularity (*arrow*). Surgery and pathology showed grade 1 (of 3) mucinous cystadenocarcinoma confined to the left ovary. As the patient was stage IA at diagnosis, her likelihood of 5-year survival was approximately 94%.

RISK FACTORS FOR OVARIAN CANCER

Ovarian cancer risk increases with age: based on 2014 observed National Cancer Institute Surveillance, Epidemiology, and End Result data, ovarian cancer incidence rates increase from 6.1 per 100,000 women ages 20 to 49, to 22.8 per 100,000 women ages 50 to 64, to 36.6 per 100,000 women ages 65 to 74.[8] Large prospective observational studies have been conducted to identify other risk factors and protective factors for ovarian cancer. One study evaluating ovarian cancer risk in the US Nurses' Health Study and Nurses' Health Study II found increased risk of ovarian cancer (ROC) associated with higher age of natural menopause and estrogen use, and lower risk associated with parity, breastfeeding, history of tubal ligation, and hysterectomy.[9] Oral contraceptive pills (OCP) use has been consistently shown to be protective against ovarian cancer.[10,11] A meta-analysis of 45 epidemiologic studies