Early detection of ovarian cancer

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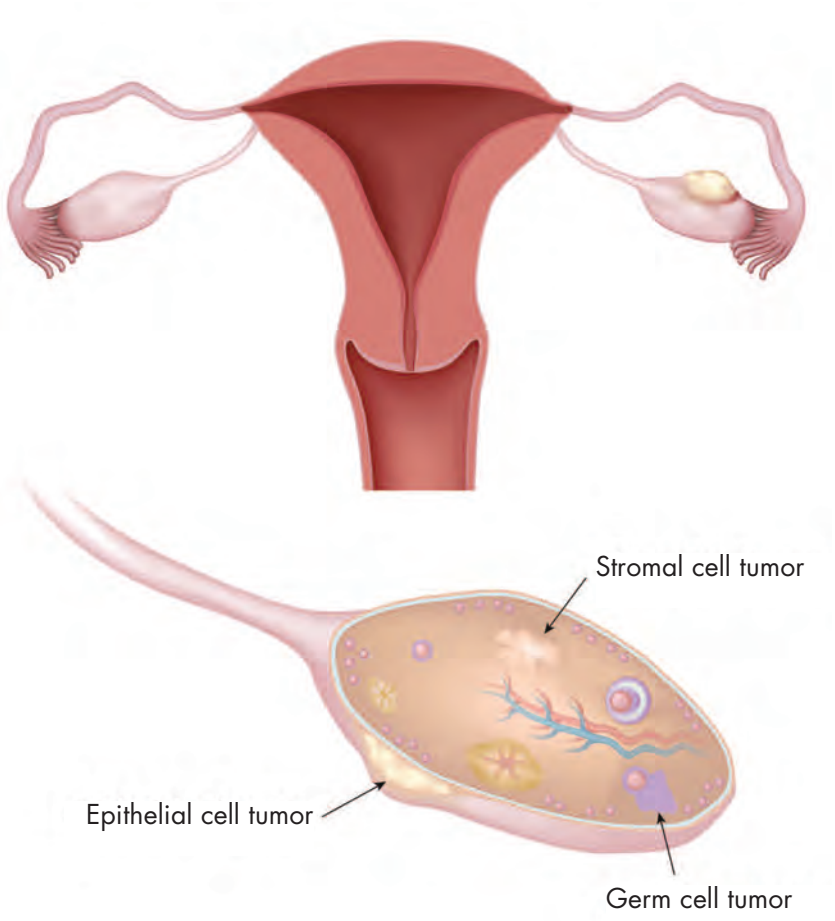
The authors searched and synthesized the literature to identify current recommendations for early detection of ovarian cancer, the female reproductive cancer with the highest mortality rate. After providing background information regarding risk factors for ovarian cancer and discussing the challenges of detecting this disease at an early stage, the authors list the most recent clinical guidelines from a variety of sources.

KEY WORDS: **ovarian cancer, early detection, risk factors, screening**



Among all female reproductive cancers, ovarian cancer has the highest mortality rate.[1-3] Although the incidence of ovarian cancer is relatively low, overall survival is only 35%.[1] In 2013, 22,240 new cases of ovarian cancer were diagnosed and 14,030 women died of the disease,[4] making it the fifth leading cause of cancer death in females, behind lung, breast, colon and pancreatic cancers.[5] Whereas earlier stage at diagnosis has been linked to an increased survival rate (70%-90%), ovarian cancer is commonly found at more advanced stages, resulting in a 5-year survival rate of only 15%.[2,6-9] Mortality reduction may be possible with earlier detection.[10]

The purpose of this article is to synthesize the literature and identify current recommendations regarding early detection of ovarian cancer. The authors searched the PubMed and CINAHL databases for primary, peer-reviewed studies reported between 2005 and 2013. This review-and-synthesis is based on 47 articles and 11 relevant clinical guidelines identified in the search.

Risk factors

Although no evidence-based ovarian cancer screening recommendations exist for women in the general population,[11] study findings indicate that women at higher risk for ovarian cancer need to be evaluated differently. Three

areas of increased risk are age, personal history, and genetics.

Age—Age is the single most important risk factor for ovarian cancer. The incidence increases significantly after menopause (average age at diagnosis, 63 years).[12]

Personal history—Some breast cancer survivors are at an increased risk for ovarian cancer; the risk is 12.7% in those with the breast cancer susceptibility gene 1 (*BRCA1*) mutation and 6.8% for those with the breast cancer susceptibility gene 2 (*BRCA2*) mutation.[13] Ovarian cancer risk after breast cancer is also higher in women with a positive family history of breast cancer.[5] Breast cancer-free women with a family history of breast or ovarian cancer but without the *BRCA1/2* mutation have a risk closer to that in the general population.[14,15] Women diagnosed with hereditary non-polyposis colorectal cancer, also known as Lynch syndrome, have a 10%-36% risk of developing ovarian cancer.[16] Other factors increasing ovarian cancer risk include endometriosis, nulliparity, infertility, early menarche, late menopause, and living in a Western industrialized nation.[13] In addition, ovarian cancer has been associated with obesity, failure to follow a low-fat diet, use of fertility drugs or androgens, and use of unopposed estrogens after menopause, although no studies have proved causation in these cases.[5]

Genetic risk and assessment—Approximately 10% of ovarian cancer cases are related to mutation of the *BRCA1/2* gene, which can be inherited.[13] In the general population, the risk of having either mutation is 1:300 to 1:800.[13] Women of Ashkenazi Jewish descent have a 10-fold higher risk of having either mutation.[13] If a woman has a *BRCA1/2* mutation, her lifetime risk of developing ovarian cancer is 65%-74%, placing her in a high-risk category.[13] The term *hereditary breast and ovarian cancer syndrome* (HBOCS) is used to describe the tendency to develop breast and/or ovarian cancer because of an inherited *BRCA1/2* gene mutation. The American Congress of Obstetricians and Gynecologists (ACOG) has issued specific referral guidelines for women with HBOCS.[13]

More than two-thirds of all ovarian cancers are diagnosed at a later stage, when the disease has already spread to other intra-abdominal organs.

The National Cancer Center Network and the Society of Gynecological Oncology (SGO) recommend that women at risk for reproductive cancer-related genetic mutations be referred for formal genetic counseling.[17,18] Despite this advice, Levy et al[19] have reported that few primary care practitioners (PCPs) follow these referral guidelines.

Challenges of early ovarian cancer detection

Early ovarian cancer detection is challenging because symptoms are often vague, leading to misdiagnosis.[20] Screening is not recommended for the general population because of the lack of effective screening methods in this population.[11] Despite the availability of triage and referral guidelines, many women's complaints are not fully investigated or appropriately referred by the PCP.[19,21,22]

Symptoms—More than two-thirds of all ovarian cancers are diagnosed at a later stage (III or IV), when the disease has already spread to other intra-abdominal organs.[7,8] Factors contributing to late diagnosis include vague symptoms and lack of a definitive precursor lesion.[8] Many women report symptoms to their PCP a few months before diagnosis,[2] yet they are misdiagnosed 70%-75% of the time.[20] Contrary to previous thought, ovarian cancer *can* present with symptoms.[7] In fact, gastrointestinal, urinary, or gynecologic symptoms are common; complaints often include abdominal bloating, a pelvic mass, pain, or malaise.[3,7,9,23]

Usefulness of the presence of symptoms as a trigger for early screening has been evaluated. Goff et al[1] developed a symptom index based on the presence of pelvic/abdominal pain, an increase in abdominal size, bloating, and difficulty eating or early satiety. In terms of identifying early ovarian cancer, the Goff symptom index was found to have a sensitivity of 56.7%, as well as a specificity of 90% for women older than 50 years and of 86.7% for women younger than 50 years. Although several symptom indexes are being studied, evidence-

Table 1. WHO guiding principles for early disease detection[24,25]

- The condition should be an important health problem for both the individual and the community, with either a high prevalence or serious consequences.
- There should be an adequate treatment for patients with the recognized condition. In addition, early treatment should improve prognosis.
- Diagnostic and treatment facilities should be available for the condition.
- There should be a latent or early symptomatic stage that is recognizable by the patient or physician.
- There should be a test or method of examination that is suitable for screening or diagnosis. Methods of screening should have high positive predictive value, sensitivity, and specificity.
- The test should be easy and acceptable enough so that, in general, patients will consent to participating.
- The natural history of the condition should be adequately understood.
- A policy of whom to treat should be agreed upon.
- The cost of screening, diagnosis, and treatment should be economically balanced in relation to the overall health of the population and economy.
- Screening should be a continuous process.

based screening tools are still lacking at this time.

Screening tests—Although many screening tests for early detection of ovarian cancer meet many of the World Health Organization (WHO) guiding principles for early disease detection (*Table 1*),[24,25] certain challenges exist. These screening methods must also have high sensitivity, specificity, and positive predictive value (PPV).[25] With regard to ovarian cancer, screening tests need to have a sensitivity of ≥75% and a specificity of >99.6% to yield a PPV of ≥10%.[24,26] (The specificity requirement is high because of the low prevalence of ovarian cancer in the general population.) Effective screening would result in 10 exploratory surgeries for every detected cancer case, which is the minimum accepted screening requirement determined by statistical estimates.[24,26]

The low specificity, sensitivity, and PPV of bimanual pelvic examination, imaging, and tumor markers, used independently in the general population, lead to the possibility of unnecessary exploratory surgery and/or patient stress,[27] posing the risk that harm will outweigh benefits.[11] The United States Preventive Services Task Force (USPSTF) recently reviewed the evidence for ovarian cancer screening and did not recommend screening for women at average risk.[11] However, women with increased risk related to *BRCA 1/2* mutations, Lynch syndrome, or a family history of ovarian cancer should be considered for genetic counseling to further evaluate their risk.[11]

Triage techniques—Several studies have suggested improved survival if women with possible ovarian cancer are managed by a gynecologic oncologist.[28] ACOG and the SGO have issued referral guidelines: Women of all ages with ascites, evidence of metastasis, or a first-degree relative with breast or ovarian cancer should be referred to a gynecologic oncologist.[12,29] Premenopausal women should be referred only if they have a CA-125 level >200 U/mL, whereas postmenopausal women should be referred if they have any elevation in CA-125 or a nodular or fixed pelvic mass.[12,29]

Delay in diagnosis is a problem in ovarian cancer. One study showed that the median interval from first symptom to diagnosis was 74.5 days.[21] In addition, PCPs were not consistent in terms of the specialist to whom they referred patients; among the 92% of patients who were referred, only 31% were referred to a gynecologist.[21] One study showed that as a woman's age increases, the likelihood that her complaint was investigated or that she was referred decreased, contributing further to a delay in diagnosis.[22]

Discussion

Studies examining the effectiveness of various screening strategies, alone or combined with each other, are ongoing, and

Table 2. Clinical guidelines for ovarian cancer

Organization	Recommendations
American Academy of Family Physicians	**Routine screening:** Uses the USPSTF recommendation against screening for ovarian cancer in the general population. **Genetics:** Uses the USPSTF recommendation for genetic counseling and *BRCA* testing for women whose family history places them at higher risk for *BRCA1/2* mutations. Women without a family history placing them at a higher risk for *BRCA* mutations should not be referred for genetic counseling or testing.
American College of Preventive Medicine	**Pelvic examinations:** Routine pelvic exams are not recommended for screening for ovarian cancer, but they should be performed for diagnostic purposes. **CA-125:** Not recommended for asymptomatic women **USG:** Not recommended for asymptomatic women **Genetics:** Screening of women with familial cancer syndrome may be appropriate. Screening women with 0-1 first-degree relative with ovarian cancer is not recommended.
American College of Radiology Appropriateness Criteria for Ovarian Cancer Screening	**Woman with average risk:** Pelvic trans-abdominal or transvaginal ultrasonography, CT or MRI of the pelvis with or without contrast, full-body FDG-PET, or pelvic USG with Doppler is usually not appropriate. Doppler USG is often helpful to evaluate blood flow but has not proved helpful in normal ovaries. **High-risk premenopausal women due to personal or family history of cancer:** Pelvic transvaginal USG is usually appropriate, but women should be informed that there is no proven screening benefit. Doppler USG may be appropriate to evaluate blood flow in an ovarian mass. Pelvic transvaginal and Doppler USG become more appropriate if a woman has an elevated CA-125. Pelvic USG may be appropriate. MRI or CT of the pelvis with or without contrast or full-body FDG-PET is not recommended.
American Congress of Obstetricians and Gynecologists and Society for Gynecologic Oncologists	**Genetics:** • **Risk assessment is recommended for women with a 20%-25% risk for inherited breast and ovarian cancer.** These women include those with a personal history of both breast and ovarian cancer; those with ovarian cancer and a close relative with ovarian cancer, premenopausal breast cancer, or both; Ashkenazi Jewish women with ovarian cancer or breast cancer at age 40 years or younger; those aged 50 years or younger and a close relative with ovarian cancer or male breast cancer; and those with a close relative having a *BRCA1/2* mutation. • **Risk assessment may be helpful for women with a 5%-10% risk for inherited breast and ovarian cancer.** These women include those with breast cancer at age 40 years or younger; those with ovarian cancer, primary peritoneal cancer, or fallopian tube cancer of high grade, serous histology at any age; those with bilateral breast cancer (especially if diagnosed at age ≤50 years), those with breast cancer at age 50 years or younger and a close relative with breast cancer at age 50 years or younger; those with breast cancer at any age and two or more close relatives* with breast cancer at any age (especially if at least one case of breast cancer was diagnosed at age 50 years or younger); and unaffected women with close relatives meeting the criteria above. **Triage:** Transvaginal USG is the imaging modality of choice for a pelvic mass. Simple cysts up to 10 cm in diameter are almost always benign, even in postmenopausal patients. • **Premenopausal women**: Refer premenopausal women to a gynecologic oncologist when there is an elevation of CA-125 >200 U/mL, ascites, evidence of metastasis by exam or imaging, or family history of breast or ovarian cancer in a first-degree relative. • **Postmenopausal women**: Any CA-125 elevation in a postmenopausal woman has a high suspicion for malignancy. Therefore, refer postmenopausal women to a gynecologic oncologist if these women have elevated CA-125 levels, ascites, nodular or fixed pelvic mass, evidence of metastasis by exam or imaging, or family history of breast or ovarian cancer in a first-degree relative.

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Table 2. (continued)

Organization	Recommendations
Agency for Healthcare Research and Quality	**Genetics:** Further research needs to be performed using appropriately designed studies before genetic testing can be recommended because the clinical utility of changing management based on tests has not been thoroughly evaluated. There is promising research, but the studies have been biased or limited.
American Medical Association	**Genetics:** Early screening for breast and ovarian cancer could benefit women with *BRCA1* mutations. Early screening for breast cancer could benefit women with *BRCA2* mutations.
National Comprehensive Cancer Network	**Symptomatic women:** Women with a palpable pelvic mass having symptoms of ascites, abdominal distention, bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, or urinary urgency or frequency, without another source of malignancy, should have an abdominopelvic exam, USG and/or abdominal/pelvic CT, chest imaging, complete blood cell count, and liver function tests. A CA-125 or other tumor marker measurement, gastrointestinal evaluation, or evaluation of family history should be considered. **Genetics:** Criteria for further risk evaluation by a genetics specialist include at least one of the following: *In an affected individual:* (a) known breast cancer genetic mutation in the family, (b) breast cancer before age 50, (c) triple negative breast cancer, (d) two breast cancer primaries in the individual, (e) breast cancer and one or more close relatives with early breast cancer, epithelial ovarian cancer, or two close relatives with breast cancer and/or pancreatic cancer at any age, or from an increased-risk population, (f) at least one family member with breast cancer and pancreatic cancer, aggressive prostate cancer, sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma, thyroid cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of GI tract, diffuse gastric cancer, (g) ovarian cancer, (h) male breast cancer *In an unaffected individual:* a family history of one or more of the following: (a) known breast cancer genetic mutation in the family, (b) at least two breast primaries in a single individual, (c) at least 2 individuals with breast primaries on the same side of the family, (d) at least one ovarian cancer primary from the same side of the family, (e) first- or second-degree relative with breast cancer at age 45 years or younger, (f) at least one family member on the same side of the family with a combination of breast cancer and at least one of the following: pancreatic cancer, aggressive prostate cancer, sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma, thyroid cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of GI tract, diffuse gastric cancer, (g) male breast cancer
Society of Gynecologic Oncologists	**Genetics:** Women at risk for hereditary breast and ovarian cancer syndromes should be identified, assessed, and counseled about obtaining genetic tests. **Serum biomarkers:** Tumor marker panels have not been adequately evaluated and have not yet proved to improve early detection of ovarian cancer.
United States Preventive Services Task Force	**Genetics:** The low population prevalence of ovarian cancer would produce a low yield from routine screening, but women at high familial risk may benefit from screening. **Routine screening:** Routine screening for ovarian cancer is not recommended. There is fair evidence for early detection using CA-125 or transvaginal USG, but it would have very little effect on mortality. The harms of diagnostic procedures outweigh the benefits of screening (grade D recommendation).

*A close relative is defined as a first-, second-, or third-degree relative.

CT, computed tomography; FDG-PET; fluorodeoxyglucose positron emission tomography; GI, gastrointestinal; MRI, magnetic resonance imaging; USG, ultrasonography; USPSTF, United States Preventive Services Task Force.

several clinical assessment tools are being evaluated for the earlier assessment of ovarian cancer. Each of these methods used in early detection of ovarian cancer is subject to WHO screening criteria (ie, sensitivity ≥75% and specificity >99.6% to yield a PPV of ≥10%).[24,26] Although many detection methods meet some of these criteria, few fulfill all requirements for non-high-risk women. Therefore, this review supports the USPSTF conclusion that sufficient evidence is lacking to recommend ovarian cancer screening for the general population.[11] Existing guidelines are outlined in *Table 2*.

Despite the USPSTF conclusion, certain specific situations place women in high-risk categories that may still benefit from early detection measures.[13,30] Nurse practitioners should be aware of what constitutes higher risk for ovarian cancer (e.g., certain genetic mutations, family history). If a woman has familial and other risk factors, NPs should offer her the option of genetic counseling.[18] Current imaging standards support the use of transvaginal ultrasonography for initial evaluation of ovarian masses.[12] Other modalities, such as computed tomography and magnetic resonance imaging, are used by specialists to evaluate an ovarian mass preoperatively. NPs should know that an elevation of CA-125 has more clinical significance in postmenopausal women than in premenopausal women.

Conclusion

Ovarian cancer is not always silent, and may manifest with gastrointestinal or other vague symptoms. Although screening the general population is not recommended, NPs need to know what places a woman at high risk for ovarian cancer and keep ovarian cancer on the differential diagnosis list in such a case. For primary care NPs, this type of triage may result in shorter delay in referral to a gynecologic oncology specialist.

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tation, certification, and education—can contribute to improved health outcomes and lower costs by improving access to care and supporting quality improvement and patient safety activities.

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Ovarian Cancer

(continued from page 13)

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