Screening for ovarian cancer

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Literature review current through: **Sep 2024.**
This topic last updated: **Feb 29, 2024.**

INTRODUCTION

In this topic, we use the term "woman/en" to describe genetic females. However, we recognize that not all people with ovaries identify as female, and we encourage the reader to consider transgender and gender nonbinary individuals as part of this larger group.

Screening for ovarian cancer first starts with a family history to identify high- versus average-risk women. Potential options for subsequent ovarian tumor screening include the serum tumor marker (cancer antigen [CA] 125) and transvaginal ultrasonography (TVUS). However, in average-risk women, there is no evidence to support a benefit from ovarian cancer screening with CA 125 or TVUS, as these screening strategies have not been shown to reduce mortality and are associated with a high rate of false-positive results and a risk of harm from subsequent invasive testing. Thus, in individuals at average risk, we recommend against screening for ovarian cancer.

This topic reviews screening for ovarian cancer in asymptomatic patients. The clinical manifestations of epithelial ovarian cancer and diagnostic testing for ovarian cancer in patients with nonspecific symptoms that may be associated with ovarian cancer are discussed separately.

- (See "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Clinical features and diagnosis".)
- (See "Early detection of epithelial ovarian cancer: Role of symptom recognition".)

Genetic counseling for those at high risk for ovarian cancer and surveillance of patients who have had ovarian cancer or prior risk-reducing bilateral salpingo-oophorectomy (rrBSO) are also described separately.

- (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes".)
- (See "Risk-reducing salpingo-oophorectomy in patients at high risk of epithelial ovarian and fallopian tube cancer", section on 'Follow-up'.)

EPIDEMIOLOGY

The lifetime risk of ovarian cancer in the general population is approximately one percent [1]. The epidemiology of ovarian cancer is discussed separately. (See "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Incidence and risk factors", section on 'Incidence'.)

A genetic predisposition (eg, *BRCA1, BRCA2*, Lynch syndrome, or others) is known to be present in about 10 percent of patients with ovarian cancer. In one study, the risk for ovarian cancer among those with *BRCA1* was 39 to 65 percent, with *BRCA2* 11 to 37 percent, and with Lynch syndrome 3 to 33 percent [2]. (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes".)

There are other factors that increase risk for ovarian cancer (eg, advancing age and certain genetic, endocrine, reproductive, and environmental factors) as well as some factors that reduce risk for ovarian cancer. These factors are described in detail separately. (See "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Incidence and risk factors" and "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Incidence and risk factors", section on 'Protective factors'.)

LIMITATIONS AND CHALLENGES OF SCREENING

Potential benefits — To reduce ovarian cancer mortality, a screening program would need to detect ovarian cancer at an early stage, because with current treatment methods, ovarian cancer mortality is closely related to stage at diagnosis (table 1). The poor overall survival rate is in large part because most patients have spread of cancer beyond the ovary at the time of clinical detection. (See "Overview of epithelial carcinoma of the ovary, fallopian tube, and peritoneum", section on 'Prognosis'.)

Early detection efforts with imaging focused only on the ovaries may miss many tumors [3]. A model of unifocal disease beginning in the ovaries and progressing to diffuse disease is plausible. However, it has been proposed that a substantial number of ovarian cancers may be multifocal and extra-ovarian (ie, originating in the fallopian tube) at their earliest recognizable state; carcinomatosis has been seen to develop even after the removal of normal ovaries [4]. Little is known about the mechanism or timing of progression from localized to disseminated ovarian cancer.

Potential harms — The potential harms associated with screening for ovarian cancer include risks of false-positive results, psychological stress, and surgical risks.

Positive screening tests for ovarian cancer may lead to surgical evaluation (eg, laparoscopy or laparotomy). Surgical procedures are associated with physical and psychological morbidity, including a small risk for serious complications due to the surgical procedure (eg, postoperative infection), risks of anesthesia for the procedure, a postoperative recovery period, and substantial financial costs.

Because ovarian cancer has a low prevalence, the rate of false-positive results will be high unless a screening program has a high specificity. With a high false-positive rate, many patients will be subjected to unnecessary surgery. Most experts feel that a screening program for ovarian cancer should have a positive predictive value (PPV) of at least 10 percent, so that for each screen-detected ovarian cancer, no more than nine women undergo unnecessary procedures for false-positive results [5-7]. A PPV of at least 10 percent requires specificity of at least 99.6 percent, assuming a sensitivity of 80 percent for screening for all women age >50 years.

Available tests do not meet these criteria. In the Prostate, Lung, Colon, Ovarian (PLCO) Cancer Screening Trial, approximately five percent of patients had false-positive results at each round of screening (3285 patients), and one-third of patients with false-positive results (1080 patients) had surgical follow-up [8]. Fifteen percent (166 patients) who had surgery for a false-positive finding experienced at least one serious complication (21 complications per 100 surgical procedures).

Patients with abnormal results on screening tests may also experience adverse psychological effects (eg, anxiety) related to diagnostic uncertainty.

LACK OF BENEFIT OF SCREENING STRATEGIES

Tests evaluated for screening have not detected ovarian cancer at an early enough stage to reduce mortality and have led to unnecessary surgical procedures for false-positive results.

Cancer antigen 125 (CA 125) — CA 125, an ovarian cancer tumor marker, did not reduce mortality due to ovarian cancer when studied as a possible screening test in the randomized Prostate, Lung, Colon, Ovarian Cancer (PLCO) Cancer Screening Trial [9].

Studies show CA 125 may predict ovarian cancer, but its usefulness is hampered by its limited specificity and very low positive predictive value (PPV). In a prospective study of asymptomatic postmenopausal women, elevated CA 125 (≥30 Units/mL) was a predictor of subsequent ovarian cancer risk (relative risk [RR] 35.9 and 14.3 at one and five years, respectively) [10]. However, in the PLCO Cancer Screening Trial, 74 percent of the CA 125-detected ovarian cancers were at an advanced stage (stage IIIC or IV) [11].

Annual CA 125 testing alone lacks sufficient specificity for screening in average-risk patients. Specificity is limited because a variety of benign and malignant gynecologic and non-gynecologic conditions elevate CA 125 (table 2 and figure 1), leading to false-positive results. CA 125 is elevated in approximately 1 percent of healthy women, fluctuates during the menstrual cycle, increases with age, and varies with ethnicity and smoking status [12,13]. Premenopausal women especially have a higher likelihood of benign gynecologic conditions; however, PPV is unacceptably low even in postmenopausal women. In three large screening studies, specificity of a single CA 125 for detection of ovarian neoplasms in postmenopausal women ranged from 98.6 to 99.4 percent, resulting in a low PPV of 3 percent [14-16]. In the PLCO Cancer Screening Trial, among healthy women ages 55 to 74 years, PPV for invasive cancer was similarly low [11,17,18].

The change in CA 125 levels over time appears to be more informative, but this approach is not generally used for screening. A large prospective study in 9233 postmenopausal women, with measurements of CA 125 at two or more times, used a modeling method to estimate risk of ovarian cancer [19]. The model incorporates age-specific incidence of cancer, absolute CA 125 level, and rate of change over time. Compared with a specific cutoff value of CA 125, the model improved sensitivity for detection of ovarian cancer from 62 to 86 percent when specificity was fixed at 98 percent. An algorithm (Risk of Ovarian Cancer Algorithm [ROCA]) incorporating change in CA 125 measurements over time was used as part of multimodal screening in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) [20,21]. (See 'Multimodal (CA 125 and TVUS) tests' below.)

The use of CA 125 to evaluate an adnexal mass is described separately. (See "Adnexal mass: Role of serum biomarkers in diagnosing epithelial carcinoma of the ovary, fallopian tube, or

peritoneum", section on 'Cancer antigen 125'.)

Transvaginal ultrasound (TVUS) — In the aggregate, studies do not suggest that screening with TVUS reduces ovarian cancer mortality [22-25].

The sensitivity of TVUS is in part observer-dependent and has ranged from 80 to 100 percent in studies of women with clinically detected ovarian cancer and in several prospective screening studies [26]. Specificity has ranged from 94 to 99 percent in screening studies, including two studies of TVUS for women with a family history of ovarian cancer [27,28].

A large randomized trial of women aged 50 to 74 years who did not have increased risk of familial ovarian cancer found that screening with TVUS did not reduce mortality. The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) included 50,623 women who had annual TVUS [21,23,24]. Initial screening detected 45 primary ovarian and tubal cancers in the TVUS group: 13 invasive cancers were stage III or higher, 12 were stage I or II, and 20 were borderline tumors of low malignant potential. For primary ovarian and tubal cancer, sensitivity was 84.9 percent, specificity 98.2 percent, and PPV 5.3 percent. For primary invasive cancer, sensitivity was 75 percent, specificity 98.2 percent, and PPV 2.8 percent [23]. After a median of 16.3 years of follow-up (approximately nine years after the final annual screening), ovarian and tubal cancers were diagnosed in 1 percent of both the unscreened and the TVUS arms [21]. There were a similar percent of cancers diagnosed at an earlier stage in the TVUS compared with the no-screening arm (stage I/II, 30 versus 28 percent; stage III/IV, 69 versus 71 percent), and there was no ovarian cancer mortality reduction associated with TVUS screening (0.6 percent mortality in both groups) [21].

By contrast, one observational study did show improved 5, 10, and 20-year disease-specific survival associated with annual TVUS [29]. However, there may have been study biases related to the nonrandomized design [25]. Additionally, these results reflect findings from a single center with high expertise in ultrasound that may not be reproducible in the general community.

Ultrasonography for screening also appears to perform poorly in women at high risk of ovarian cancer. In the National Ovarian Cancer Early Detection Program, 4526 women at high risk for ovarian cancer based on a personal or family history of ovarian or breast cancer, other cancer syndromes, or the presence of a *BRCA* mutation were screened with TVUS every six months [22]. All cancers (two ovarian, four peritoneal, and four fallopian tube) detected by ultrasonography during the screening period were stage III.

Multimodal (CA 125 and TVUS) tests — The effectiveness of multimodal screening using a combination of CA 125 and TVUS have been evaluated in randomized trials and observational

studies [8,21,24,30]. Two strategies have been examined: the performance of both tests for all screened participants (concurrent testing) and CA 125 testing in all participants followed by TVUS only on patients with abnormal CA 125 (sequential testing).

- **Concurrent testing with CA 125 and TVUS** – Concurrent multimodal screening has been evaluated in both average- and high-risk populations:

  - **Average risk** – The PLCO Cancer Screening Trial found that screening using both CA 125 and TVUS at annual intervals did not reduce mortality in the general population [8,18]. The PLCO Cancer Screening trial included postmenopausal women aged 55 to 74 years who were assigned to screening annually with CA 125 for six years and TVUS for four years or to usual care. Usual care and management of abnormal screening results were at the discretion of their usual clinician. Participants were followed for a median 12.4 years, and the trial was stopped prior to scheduled completion because the monitoring board determined futility. The mortality rate due to ovarian cancer was similar in screened and usual care groups: 3.1 versus 2.6 per 10,000 person-years (rate ratio 1.18, 95% CI 0.82-1.71). At initial screening, 29 tumors were detected; 20 of those were invasive, with 18 of these at stage III or IV. Compared with usual care, the incidence of ovarian cancer was not different for women screened, and there was no difference in the proportion of patients with advanced disease (stage III or IV), 77 versus 78 percent.

  - **High risk** – Studies of concurrent testing with CA 125 and TVUS in high-risk patients are largely limited to observational studies and have found that most detected cancers (70 to 80 percent) are stage III or IV [2,31]. In the United Kingdom Familial Ovarian Cancer Screen Study (UK FOCSS) that included 3563 women with a familial ovarian cancer syndrome who had declined or deferred risk-reducing salpingo-oophorectomy (rrSO), participants were screened annually for a mean of 3.2 years with a combination of TVUS and CA 125 [2]. The sensitivity for incident ovarian cancer/fallopian tube cancer was 81.0 to 87.5 percent, depending on whether occult cancers detected at the time of rrSO in women who underwent the procedure prior to the end of the study period were classified as false negative or true positive. The PPV of incident screening was 25.5 percent, which exceeds the threshold of 10 percent considered necessary for ovarian cancer screening. Four women underwent surgery for each case of detected cancer. Women who had not been screened in the year before cancer diagnosis were more likely to have stage IIIC or higher cancer than women screened in the preceding year (86 versus 26 percent); detection of lower-stage disease in women who adhered to

screening led to a decision to decrease the screening interval to four months for the next phase of the study.

- **Sequential testing (CA 125-triggered TVUS)**

  - **Average risk** – In the UKCTOCS trial including postmenopausal women aged 50 to 74 years, an early mortality benefit was suggested for average-risk women screened with annual CA 125, followed by TVUS if the CA 125 result was abnormal as determined by an algorithmic guideline based on an individual's change in serial levels (ROCA) [20,24]. However, after a median follow-up of 16 years (approximately nine years following the end of annual screening), there was no difference in ovarian cancer mortality between those undergoing multimodal screening compared with no screening (0.6 percent in each group) [21].

    At 16 years' follow-up, among those undergoing multimodal screening, there was an increase in the percentage of cancers diagnosed at stage I and II and a decrease in those diagnosed at stage III and IV compared with those having no screening (39 percent increase and 10 percent decrease, respectively). As above, in this longitudinal study, diagnosis at an earlier stage was not associated with a reduction in ovarian cancer mortality.

In the United States, sequential testing has been evaluated as part of a two-stage strategy in the Normal Risk Ovarian Cancer Screening Study (NROSS) [30]. In this study conducted among 7,856 average-risk women, rising serum CA125 (analyzed with the ROCA) prompted TVUS, and abnormal ultrasound results prompted surgery to detect ovarian cancer. In 21 years of follow-up, 34 patients were referred for surgery, and 15 ovarian cancers and two borderline tumors were detected. Early stage (I-II) cancers accounted for 70 percent of ovarian cancers detected by screening. The sensitivity for detecting ovarian and borderline cancer was 74 percent, and the PPV was 50 percent.

  - **High risk –** Observational studies of women with BRCA mutations who elect to defer risk-reducing salpingo-oophorectomy and undergo surveillance with the ROCA every four months are in progress [32,33]. (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes".)

Other testing

- **Pelvic examination** – Studies have found no data to support the use of the pelvic examination to screen for ovarian cancer in asymptomatic, average-risk women [8,34,35].

Ovarian tumors are rarely found at an early stage during bimanual pelvic examination due to the deep anatomic location of the ovary. Tumors are occasionally detected; however, they are usually at an advanced stage and associated with a poor prognosis [36]. Lack of benefit of pelvic examination for ovarian cancer mortality reduction is discussed separately. (See "The gynecologic history and pelvic examination", section on 'Indications and frequency for examination'.)

- **Papanicolaou (Pap) testing** – The Pap test does not generally detect ovarian cancer, although it may occasionally reveal malignant ovarian cells [37]. (See "Cervical cancer screening: The cytology and human papillomavirus report", section on 'Other types of malignancy'.)

  Methods to use genetic analysis and different sampling techniques when obtaining a Pap test are being explored [37].

- **Ovarian cancer symptom index** – A set of structured questions called the ovarian cancer symptom index is not recommended for routine clinical use for screening. The symptom index was found to have low specificity and a very low PPV for ovarian cancer [38,39]. The index and follow-up for a positive result are discussed separately. (See "Early detection of epithelial ovarian cancer: Role of symptom recognition", section on 'Symptom index'.)

- **Other tumor markers** – In addition to CA 125, other markers (eg, human epididymis protein 4 [HE4], carcinoembryonic antigen [CEA], and cancer antigen 19-9 [CA 19-9] are being investigated. (See "Adnexal mass: Role of serum biomarkers in diagnosing epithelial carcinoma of the ovary, fallopian tube, or peritoneum", section on 'Biomarkers'.)

  Some studies suggest that combinations of biomarkers may improve ovarian cancer detection, though further studies are needed to validate the findings. A multi-analyte blood test (not commercially available) for genetic alterations and tumor-specific biomarkers had high sensitivity (98 percent) and specificity (>99 percent) for detection of ovarian cancer at an early stage [40]. Some studies found that biomarkers (eg, CA 125, HE4, and others) may be used as a panel or in combination with epidemiologic risk factors to identify women at higher risk for ovarian cancer [41,42]. By contrast, compared with CA 125 testing alone, a panel of different proteomic biomarkers did not increase the sensitivity for ovarian cancer [43].

  Use of biomarker panels in the evaluation of patients with an adnexal mass is described separately. (See "Adnexal mass: Role of serum biomarkers in diagnosing epithelial carcinoma of the ovary, fallopian tube, or peritoneum", section on 'Biomarker panels for patients undergoing surgery'.)

SCREENING APPROACH

Family history — A family history is essential to identifying patients with a potential hereditary (eg, familial) cancer syndrome.

Specific details to obtain when questioning the patient include family history of ovarian or breast cancer, whether the patient is of Ashkenazi Jewish descent, and whether the family or patient is known to have a hereditary cancer syndrome (eg, *BRCA1, BRCA2*, Lynch syndrome, or others) that places the patient at high risk for ovarian cancer. (See "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Incidence and risk factors", section on 'Genetic factors'.)

High-risk family history — Patients identified with a high-risk family history that suggests a possible hereditary syndrome for ovarian cancer should be referred to a genetic counselor. Genetic counseling includes a discussion of genetic screening for a possible hereditary cancer syndrome (eg, *BRCA1*, *BRCA2,* Lynch syndrome, and other mutations) [44,45]. Patients who test positive for one of these syndromes may benefit from specific interventions such as risk-reducing bilateral salpingo-oophorectomy (rrBSO) to reduce risk.

The approach to counselling and testing for different genes associated with hereditary cancer syndromes for ovarian cancer and the subsequent management of these patients, whether they test positive or negative, are discussed in detail separately. (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes".)

Lower-risk family history — A patient may have a history (eg, a remote family member with ovarian cancer, without evidence of a hereditary pattern) that increases risk to a lesser extent than a hereditary cancer syndrome. Patients may have other risk factors for ovarian cancer as well. (See "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Incidence and risk factors", section on 'Probable risk factors'.)

When there is a family history without evidence for a hereditary cancer syndrome, there is no evidence that screening is effective and screening is generally not advised. Any decision to offer screening in this setting requires a careful discussion of the limited evidence for benefit and the potential for harm from false-positive results.

Average-risk patients — In asymptomatic women at average risk (without a genetic predisposition or family history of ovarian cancer), we recommend against screening for ovarian cancer [46]. Based on the available data, there is no evidence that the benefits of screening for ovarian cancer outweigh the harms related to the adverse effects of following up

on findings that turn out to be false positives. (See 'Lack of benefit of screening strategies' above.)

This is in concordance with the US Preventive Services Task Force (USPSTF) 2018 recommendation statement that recommends against screening for ovarian cancer for asymptomatic women who are not known to have a high-risk hereditary cancer syndrome; major professional societies have similar recommendations [47-51].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Screening for ovarian cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Ovarian cancer screening (The Basics)" and "Patient education: Genetic testing for breast, ovarian, prostate, and pancreatic cancer (The Basics)")

- Beyond the Basics topics (see "Patient education: Screening for ovarian cancer (Beyond the Basics)" and "Patient education: Genetic testing for hereditary breast, ovarian, prostate, and pancreatic cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Screening strategies** – Screening for ovarian cancer first starts with a family history to identify high- versus average-risk women. Potential options for subsequent ovarian tumor screening include serum tumor marker (cancer antigen [CA] 125) and transvaginal ultrasonography (TVUS). (See 'Introduction' above.)

  - **Potential benefits –** Ovarian cancer continues to have a high mortality rate, as most ovarian cancers are late stage at the time of diagnosis. To reduce mortality, a screening program would need to detect cancers at an early stage. (See 'Potential benefits' above.)

  - **Challenges and limitations –** Challenges to developing an effective screening strategy for ovarian cancer include that it is a low prevalence disease in average-risk women, requiring a testing strategy that has very high specificity as well as sensitivity in order to minimize false-positive tests. In addition, many ovarian cancers detected by screening tests are late stage. (See 'Limitations and challenges of screening' above.)

- **Screening approach**

  - **Family history** – A family history is essential to identifying women at high risk for a hereditary cancer syndrome. (See 'Family history' above.)

  - **Average-risk women** – In average-risk women, we recommend against screening for ovarian cancer (**Grade 1A**). No screening strategy (cancer antigen [CA] 125, transvaginal ultrasound [TVUS], or multimodal testing) has been shown to reduce mortality, and all screening strategies are associated with a high rate of false-positive results and a risk of harms from invasive testing. (See 'Average-risk patients' above.)

  - **Patients with family history** – Ovarian cancer is more prevalent among patients with a family history, in particular those with a hereditary cancer syndrome (eg, *BRCA1, BRCA2*, Lynch syndrome, or others). Such patients should be referred for genetic counseling and consideration of genetic testing and may benefit from specific risk reduction strategies such as risk-reducing bilateral salpingo-oophorectomy (rrBSO). (See 'Family history' above and "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes" and "Risk-reducing salpingo-oophorectomy in patients at high risk of epithelial ovarian and fallopian tube cancer".)

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Topic 7563 Version 68.0

GRAPHICS

Carcinoma of the ovary: Five-year survival, United States 2007-2013

Stage*	Five-year survival (%)
I	89
II	71
III	41
IV	20

* American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 6th edition.

Adapted from: Torre LA, Trabert B, DeSantis CE, et al. Ovarian cancer statistics, 2018. CA Cancer J Clin 2018; 68:284.

Graphic 134243 Version 1.0

Conditions associated with an elevated serum CA 125 concentration

Gynecologic malignancies
Endometrial cancer
Epithelial ovarian, fallopian tube, and primary peritoneal cancers
Benign gynecologic conditions
Adenomyosis
Benign ovarian neoplasms
Endometriosis
Functional ovarian cysts
Meig syndrome
Menstruation
Ovarian hyperstimulation
Pelvic inflammatory disease
Pregnancy
Uterine leiomyomas

Nongynecologic conditions
Ascites
Appendicular abscess
Cirrhosis and other liver disease
Colitis
Cystic fibrosis
Diverticulitis
Heart failure
Myocardial infarction
Myocardiopathy
Pancreatitis
Pericardial disease
Pleural effusion
Pneumonia
Pulmonary embolism
Recent surgery
Renal insufficiency
Sarcoidosis
Systemic lupus erythematosus
Tuberculosis peritonitis
Urinary tract infection
Nongynecologic cancers
Breast
Colon
Gallbladder
Hematologic malignancies
Liver
Lung
Pancreas

CA: cancer antigen.

Data from:

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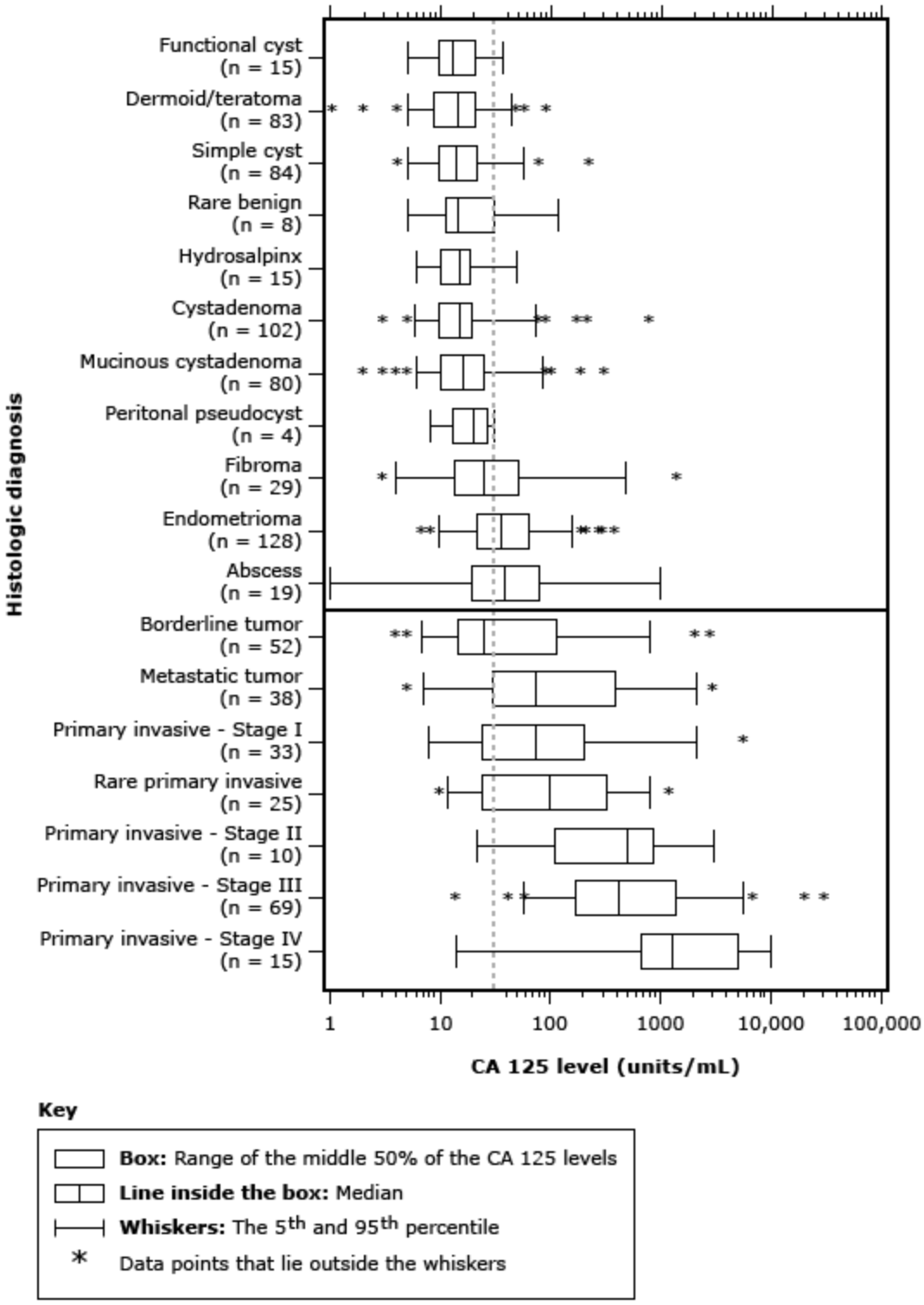
Graphic 81621 Version 8.0

Box plots showing CA 125 serum levels by histologic diagnosis of adnexal masses



CA 125: cancer antigen 125.

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Contributor Disclosures

Karen J Carlson, MD No relevant financial relationship(s) with ineligible companies to disclose. **Joann G Elmore, MD, MPH** Other Financial Interest: Elsevier [Author royalties]. All of the relevant financial relationships listed have been mitigated. **Barbara Goff, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Sara Swenson, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Alana Chakrabarti, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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