## Appendix 1. Ovarian Cancer Evidence Review Conference Attendees

<table>
<thead>
<tr>
<th>Attendee Role</th>
<th>Attendee Name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence review expert panelist</td>
<td>Joel Barkley, MD&lt;br&gt;Emily Barrows, MD&lt;br&gt;Rebecca Brooks, MD&lt;br&gt;Kimberly Gecsi, MD&lt;br&gt;Kathryn Huber-Keener, MD, PhD&lt;br&gt;Myrlene Jeudy, MD&lt;br&gt;Shirley Mei, MD</td>
</tr>
<tr>
<td>Stakeholder organization representative</td>
<td>Jeffrey Quinlan, MD, FAAFP (American Academy of Family Physicians)&lt;br&gt;Robert A. Smith, PhD (American Cancer Society)&lt;br&gt;Fatima Syed, MD, MSc (American College of Physicians)&lt;br&gt;Emma Barber, MD, MS (American College of Surgeons Commission on Cancer)&lt;br&gt;Melissa Buffalo, MS (American Indian Cancer Foundation)&lt;br&gt;Eloise Chapman-Davis, MD (American Society of Clinical Oncology)&lt;br&gt;Julianna Grandinetti, PA-C, MSPAS (Association of Physician Assistants in Obstetrics and Gynecology)</td>
</tr>
<tr>
<td>Role</td>
<td>Name</td>
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<td>-------------------------------</td>
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<tr>
<td>Advisory group member</td>
<td>William Burke, MD</td>
</tr>
<tr>
<td></td>
<td>David Chelmow, MD</td>
</tr>
<tr>
<td></td>
<td>Nicole F. Dowling, PhD</td>
</tr>
<tr>
<td>ACOG staff</td>
<td>Christopher M. Zahn, MD</td>
</tr>
<tr>
<td></td>
<td>Nancy O’Reilly, MHS</td>
</tr>
<tr>
<td></td>
<td>Julia O’Hara, MPH</td>
</tr>
<tr>
<td></td>
<td>Apurvi Shah, MPH</td>
</tr>
<tr>
<td>Consultant</td>
<td>Dana Trevas (Shea &amp; Trevas, Inc.)</td>
</tr>
<tr>
<td>Observer</td>
<td>Lisa C. Richardson, MD, MPH (CDC)</td>
</tr>
<tr>
<td></td>
<td>Ally Moehring (CDC)</td>
</tr>
<tr>
<td></td>
<td>Sherri L. Stewart, PhD (CDC)</td>
</tr>
<tr>
<td></td>
<td>Nicole Dowling, PhD (CDC)</td>
</tr>
<tr>
<td>Technical Support</td>
<td>Laarni Reyes (ACOG)</td>
</tr>
</tbody>
</table>

ACOG, American College of Obstetricians and Gynecologists; CDC, Centers for Disease Control and Prevention.

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INTRODUCTION

This document addresses the epidemiology of ovarian cancer, specifically epithelial ovarian cancer (serous, mucinous, endometrioid, clear cell, and undifferentiated) and germ cell, sex cord-stromal, and borderline tumors (also known as tumors of low malignant potential).

METHODS

The American College of Obstetricians and Gynecologists’ Resource Center searched the Cochrane, MEDLINE (through Ovid), and PubMed databases using a search strategy based on the question, “What is the epidemiology of ovarian cancer?” Results were categorized according to the following levels of evidence:

- Level I: Randomized, controlled trials (RCTs), systematic reviews, and meta-analyses
- Level II: Observational studies
- Level III: Guidelines and narrative reviews
- No level: References that were not fully indexed by level at the time of the literature search
Additional relevant guidelines from the American College of Obstetricians and Gynecologists, the US Preventive Services Task Force, the Royal College of Obstetricians and Gynaecologists, the European Society for Medical Oncology, the National Comprehensive Cancer Network, the Society of Obstetricians and Gynaecologists of Canada, the Society of Gynecologic Oncology, the American College of Radiology, the National Institute for Health and Care Excellence, and the American Society for Reproductive Medicine were identified and sorted by relevance using a search strategy focused on screening, diagnosis, and risk factors rather than treatment. A single investigator reviewed the titles and abstracts of all collected articles and guidelines. Selected manuscripts were then reviewed in full.

Inclusion criteria were major professional society or health service guidelines, systematic reviews, meta-analyses, RCTs, cohort studies, and case–control studies available in English and published between 2000 and 2021. Case reports, case series, and articles unavailable in English were excluded, as were articles from outside of countries designated very high in the United Nations Human Development Index (HDI).

Priority was given to systematic reviews and meta-analyses, and individual source studies were generally not reviewed separately unless they contained additional pertinent information not otherwise found in the review. Nonsystematic review articles were generally excluded except when high-quality studies could not be found for a specific topic.

RESULTS

Literature Summary

The initial literature review identified 1237 studies pertaining to the designated topics. It located 4 level I RCTs, all of which were reviewed and excluded as they did not address the relevant topic. A total of 19 level 1 meta-analyses or systematic reviews were found, and, after review, one was included. The excluded studies did not fulfill the eligibility criteria of the reviewers. The authors provided this information as a supplement to their article.
criteria or answer the intended questions. Of the 246 level II studies reviewed, three were included and the remainder excluded. The 72 level III studies were reviewed and two were included. Of the 246 studies without an associated level, all were reviewed and ten were included. The 49 assorted studies from PubMed (all levels) were reviewed, and two were included. Another 112 studies from PubMed without a designated evidence level were reviewed and excluded. Finally, 31 publications from various professional organizations were reviewed, and five were included. An additional three studies were identified by the primary reviewer while evaluating references and via PubMed and were included. A total of 26 studies were included in the final review.

**Summary of Data**

**Overview**

Ovarian cancer is relatively rare, ranking 17th among all cancers in the United States, with an incidence of 10.6/100,000 women per year from 2014 to 2018.1,2 Despite this incidence, ovarian cancer is the fifth most common cause of cancer death among women in the United States (following lung, breast, colon, and pancreatic cancers) and is the most deadly gynecologic cancer.3,4 The lifetime risk of developing ovarian cancer over a 95-year lifespan is about 1.1%. In 2018, there were 235,081 women living in the United States with the disease.2 It is estimated that 19,880 new cases will occur in 2022, accounting for 2.1% of female cancer diagnoses and 17.3% of gynecologic cancers in the United States.2 It is estimated that 12,810 women will die from ovarian cancer in the US in 2022.4

One reason for the high mortality rate is the indolent nature of the symptoms associated with ovarian cancer. As a result, stage at diagnosis is typically quite advanced, with only 19% of cases localized on presentation and 50% of cases presenting with distant disease.4 Overall 5-year survival in the United States is 49.7% and is strongly correlated with...
stage at the time of diagnosis. Five-year survival is 93.1%, 74.2%, 30.8%, and 28.2% when stage at the time of diagnosis is localized, regional, distant, and unstaged, respectively. Similarly, the chance of recurrence correlates heavily with stage at diagnosis. Fewer than 10% of women with stage I disease will have recurrence, whereas 90% of stage IV disease will recur.

About 10% to 25% of ovarian cancers are associated with a hereditary genetic abnormality. While there are multiple germline mutations associated with ovarian cancer, BRCA1 and BRCA2 germline mutations are the most common and are found in 13% to 15% of women with ovarian cancer, and somatic mutations are found in another 7% of women with ovarian cancer. A woman with a BRCA1 mutation has a 15% to 45% lifetime risk of ovarian cancer, whereas for a woman with BRCA2 mutation, this risk is about 10% to 20%.

Ovarian cancers are subdivided by histology, of which there are three main types: epithelial, germ cell, and sex cord-stromal. Epithelial ovarian cancer is by far the most common, accounting for 90% of malignant ovarian neoplasms. The histologic subtypes of epithelial ovarian cancers are serous, endometrioid, mucinous, clear cell, undifferentiated, and tumors that are borderline tumors or of low malignant potential. Given the differences in how these histologies behave, they can also be divided into two main subtypes, types I and II. Type I cancers are typically more indolent, growing locally and metastasizing late. Type I includes the low-grade serous and endometrioid, clear cell, and mucinous cancers. Type II cancers are more aggressive and tend to be advanced at diagnosis; they include high-grade serous carcinoma, carcinosarcoma, and the undifferentiated cancers. The nonepithelial histologies include germ cell tumors, which account for about 5%, and sex cord-stromal tumors, which account for 3% to 5%, both of which can be further subdivided into more specialized histologies (see Box 1).
Box 1. Ovarian Cancer Types*

<table>
<thead>
<tr>
<th>Epithelial Ovarian Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous carcinoma</td>
</tr>
<tr>
<td>♦ High-grade serous carcinoma</td>
</tr>
<tr>
<td>♦ Low-grade serous carcinoma</td>
</tr>
<tr>
<td>Endometrioid carcinoma</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
</tr>
<tr>
<td>Borderline or low-malignant-potential neoplasms</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
</tr>
<tr>
<td>Undifferentiated or dedifferentiated</td>
</tr>
<tr>
<td>Transitional cell carcinoma (Brenner tumor)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Germ Cell Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgerminoma</td>
</tr>
<tr>
<td>Immature teratoma</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
</tr>
<tr>
<td>Endodermal sinus or yolk sac tumors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex Cord-Stromal Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulosa cell tumors</td>
</tr>
<tr>
<td>Thecomas</td>
</tr>
<tr>
<td>Sertoli-Leydig cell tumors</td>
</tr>
</tbody>
</table>


https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf; The distal fallopian tube as the origin of non-uterine
The authors provided this information as a supplement to their article.
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The carcinogenesis of these myriad ovarian malignancies has long been debated, but since 2000, the scientific community has developed a new understanding that high-grade serous carcinomas, which represent the overwhelming majority of ovarian cancers, arise not from the ovary but from the fallopian tube.9 Although the term “ovarian cancer” is used throughout this review, it is important to acknowledge that ovarian cancer represents a constellation of malignancies involving the ovary, the peritoneum, and the fallopian tube.

**Age**

With some exceptions, ovarian cancer is generally a disease of older age, with over 88% of cases diagnosed after age 45.2,8,12 For children and young adults, the incidence of malignant ovarian cancer of any type is very low. Girls ages 14 years and younger have an incidence of only 3.7 cases per 1,000,000 females, those ages 15–19 years have an incidence of 13.7/1,000,000, and those ages 20–24 years have an incidence of 17.3/1,000,000.13 Overall incidence of ovarian cancer increases over a woman’s lifetime, peaking in the seventh decade of life, with a median age at diagnosis of 63 years.2,3 The peak incidence by age varies significantly by histologic type. The peak incidence of germ cell ovarian cancers occurs in the second decade of life, and that of sex cord-stromal ovarian cancers occurs in the sixth decade, while Burke W, Barkley J, Barrows E, Brooks R, Gesci K, Huber-Keener K, et al. Executive Summary of the Ovarian Cancer Evidence Review Conference. Obstet Gynecol 2023;142. The authors provided this information as a supplement to their article. ©2023 The Authors.
epithelial ovarian cancer, by far the most common histologic type, shows a peak incidence in the seventh and eighth decades.  

In those with epithelial ovarian cancer, increasing age is not only associated with increasing incidence of disease, but also with a higher stage at diagnosis and worse mortality. When women are categorized by age—very young (<30 years old), young (30–60 years old), and older (over 60 years old)—the percentage of ovarian cancer diagnosed at stage I or stage II is 65.3%, 40.2%, and 22.5%, respectively. Additionally, across all stages of diagnosis, younger women have a survival advantage that persists after adjusting for race, stage, grade, and surgical treatment. Very young women have a 78.8% 5-year survival rate, young women have a 58.8% survival rate, and older women have a 35.3% survival rate.  

**Race and Ethnicity**

When incidence of ovarian cancer is evaluated by race and ethnicity, historically, White women have the highest age-adjusted incidence. However, from 2015 to 2019 in the United States, non-Hispanic American Indian and Alaska Native women had the highest incidence, with 11.4 cases per 100,000 women. They are followed by non-Hispanic White women, who had 11 cases per 100,000 women; non-Hispanic Asian and Pacific Islander women, with 9.4 cases per 100,000 women; and non-Hispanic Black women, with 9 cases per 100,000 women. Hispanic women of any race have a 10.3/100,000 5-year age-adjusted incidence of ovarian cancer. Five-year age-adjusted mortality rates from 2015 to 2019 in the United States show White women experience the highest mortality, with 6.9 deaths per 100,000 women, followed by non-Hispanic Black women, with 5.9/100,000; Hispanic women (any race), with 5.0/100,000; and non-Hispanic Asian and Pacific Islander women, with 4.4/100,000. Table 1 describes the risk of being diagnosed with and dying from ovarian cancer over a lifetime, stratified by race and ethnicity.
Table 1. US Lifetime Ovarian Cancer Risk by Race and Ethnicity*

<table>
<thead>
<tr>
<th>Race or Ethnicity</th>
<th>Risk of Diagnosis (%)</th>
<th>Risk of Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All races and ethnicities</td>
<td>1.131</td>
<td>0.812</td>
</tr>
<tr>
<td>White</td>
<td>1.157</td>
<td>0.852</td>
</tr>
<tr>
<td>Black</td>
<td>0.883</td>
<td>0.668</td>
</tr>
<tr>
<td>Hispanic (any race)</td>
<td>1.172</td>
<td>0.713</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>1.063</td>
<td>0.636</td>
</tr>
<tr>
<td>American Indian or Alaska</td>
<td>1.142</td>
<td>0.608</td>
</tr>
</tbody>
</table>


Details by Histologic Subtypes

To understand the epidemiology of ovarian cancer more accurately, it is worthwhile to evaluate the various histologic subtypes. Serous carcinoma is the largest subset of epithelial ovarian cancer, accounting for up to 80% of epithelial ovarian cancers and 56.7% of all ovarian cancers. This subtype is diagnosed in older age, affects predominantly White women, has distant metastases present at diagnosis in 72% of cases, and has an overall poor prognosis. Serous carcinoma can be categorized as high grade or low grade depending on the severity of cytologic atypia and mitotic rates. Only about 10% of serous cancers are low grade, and these tend to be diagnosed at a younger age and associated with longer survival.8
Endometrioid carcinoma accounts for about 10% of epithelial ovarian cancers, presents in midlife, and more frequently presents in early stages, with only 43% of cases having distant disease at the time of diagnosis.8,17 These cancers can be low or high grade, and it is believed that endometriosis may have a causative association with this cancer type.8

Clear cell cancers account for about 5% of epithelial ovarian cancers, present in midlife, and are predominantly stage I at diagnosis (57%). Notably, clear cell cancers are far more common in Japan than elsewhere in the world, where they account for 30% of epithelial ovarian cancers.8,18

Mucinous carcinomas represent only about 3% of epithelial ovarian cancers. They occur in younger women, as early as age 20–40 years, but with a mean age at diagnosis in the mid-50s. Approximately 59.5% of mucinous carcinomas are diagnosed in stage I, and the 5-year survival rate is very good (80% to 90%).3,18

Borderline tumors, also called tumors of low malignant potential, are a subset of epithelial ovarian cancer (10–15%) and comprise many different histologic types, including papillary serous cystadenomas, mucinous cystadenomas, and serous cystadenomas.8,19 These tumors usually present in younger patients than a typical invasive carcinoma does; the median age at presentation is 40–44 years old. Most are localized at the time of diagnosis (~75%), and the 5-year survival rate is 80% to 95%.3,11,17

The subset of nonepithelial ovarian cancers consists of ovarian germ cell tumors and sex cord-stromal tumors. Ovarian germ cell tumors account for only 5% of all ovarian malignancies.10 Of these cancers, 91% are diagnosed in women under age 40, 61% of them are localized at the time of diagnosis, and the 5-year survival rate is 94%.20 Sex cord-stromal tumors are found in 3% to 5% of all ovarian cancers, and 90% of these are granulosa cell tumors.10 Median age at

The authors provided this information as a supplement to their article.
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diagnosis is 51 years, and 70% of newly diagnosed sex cord-stromal tumors are stage I on diagnosis. The 5-year survival rate is 88%, and the 10-year survival rate is 79%.21

**Global Epidemiology of Ovarian Cancer**

Across the world, approximately 225,500 women are diagnosed annually with ovarian cancer, resulting in 140,200 deaths. Ovarian cancer has the highest gynecologic cancer mortality rate in high-income nations and is second only to cervical cancer elsewhere in the world.5

Globally, incidence and mortality of ovarian cancer have a significant positive correlation with HDI level (see Table 2). In this context, ovarian cancer is more common in the high and very high HDI regions. In 2018, only 25% of the estimated 295,414 new cases of ovarian cancer around the world occurred in the low- to mid-HDI regions.22,23

**Table 2. Ovarian Cancer Incidence and Mortality by Human Development Index (HDI)**

<table>
<thead>
<tr>
<th>HDI</th>
<th>Incidence (per 100,000)</th>
<th>Mortality (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high</td>
<td>14.7</td>
<td>10.1</td>
</tr>
<tr>
<td>High</td>
<td>8.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Medium</td>
<td>4.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Low</td>
<td>2.9</td>
<td>2.3</td>
</tr>
</tbody>
</table>

The incidence of ovarian cancer is highest in Europe. The United Kingdom, Denmark, the Czech Republic, and Germany have the highest incidence at approximately 40–50 cases per 100,000 women. The Americas have the next highest incidence, with the United States and Canada holding the highest numbers for their region, followed by Oceana, Asia, and then Africa. In Europe and the Americas, the incidence of ovarian cancer increases with increasing age up to 80 years; in contrast, the incidence of ovarian cancer in Asia peaks around age 50–55 years and plateaus thereafter.

New cases of ovarian cancer in the United States and Europe have been falling on average 3.3% each year since 2009, and age-adjusted death rates have been falling about 2.7% annually since 2010. Conversely, cases in lower HDI nations have seen an increase in incidence and mortality mirroring recent economic growth and associated lifestyle changes.

**SUMMARY**

Ovarian cancer is only the 17th most common cancer in the United States but the fifth most deadly. Although ovarian cancer is an oncologic process that represents a collection of many different histologic subtypes, high-grade serous carcinoma is by far the most prevalent type. Overall, this cancer is difficult to diagnosis early and therefore associated with a high rate of recurrence and significant mortality. It disproportionately affects older women and, until recently, has been more dominant in high-HDI countries; however, as low-HDI nations gain economic traction and adopt lifestyles similar to those of the very-high-HDI nations, their rates of ovarian cancer are increasing.

**RESEARCH GAPS**

Overall there are good data regarding the epidemiology of ovarian cancer. However, improvements could be made with regard to the following:
1. Understanding the epidemiology of ovarian cancer in the transgender community; current data are limited to case studies.

2. Understanding the changing trends in incidence of ovarian cancer globally.

REFERENCES


6. The Distal Fallopian Tube as the Origin of Non-Uterine Pelvic High-Grade Serous Carcinomas: Green-top Guideline No. 44. *Royal College of Obstetricians and Gynaecologists (RCOG)* 2014;


INTRODUCTION

This document reviews the literature around risk factors for ovarian cancer in four broad categories: lifestyle factors (e.g., diet, physical activity), hormonal factors (e.g., age at menarche and menopause, oral contraceptive use), family health history, and prior health history. Appendix 4, Prevention and Risk Reduction, goes into more detail on interventions to reduce the risk of ovarian cancer among women at average or high risk.

METHODS

The American College of Obstetricians and Gynecologists’ Resource Center searched the Cochrane, MEDLINE (through Ovid), and PubMed databases using a search strategy based on the following questions and using the PICO format to direct the literature search:

\[ P = \text{patient, problem, or population}; \ I = \text{intervention}; \ C = \text{comparison, control, or comparator}; \ O = \text{outcome(s)} \]

1. **What lifestyle factors are risk factors for ovarian cancer? How strong are these risks?**

   **P:** Adults with ovaries (e.g., women and transgender men) with a potential lifestyle risk factor (high-fat diet, alcohol use, smoking, or talcum powder use)

   **O:** Relative risk (RR) or odds ratio (OR) of ovarian cancer, incidence of ovarian cancer

2. **What hormonal factors are risk factors for ovarian cancer? How strong are these risks?**
3. **What family health history factors are risk factors for ovarian cancer? How strong are these risks?**

**P:** Adults with ovaries and a known genetic mutation (BRCA1 and BRCA2 mutation carriers, Lynch syndrome, Cowden disease, Li-Fraumeni [TP53 carriers], Peutz-Jehgers [STK11 carriers], MUTYH-associated polyposis, other genes [ATM, BRIP1, RAD51C, PALB2, RAD51D, SMARCA4, BARD1, NBN]) or a family history of breast, colorectal, or ovarian cancer or associated cancers without an identified genetic mutation; adults with ovaries from at-risk ethnic groups (including Ashkenazi Jews)

**O:** RR or OR of ovarian cancer, incidence of ovarian cancer

4. **What prior health history factors are risk factors for ovarian cancer? How strong are these risks?**

**P:** Patients with a known prior related cancer (breast, colorectal, ovarian), infertility or prior use of fertility treatments, obesity, or endometriosis

**O:** RR or OR of ovarian cancer, incidence of ovarian cancer

Results were categorized according to the following levels of evidence:

- **Level I:** Randomized, controlled trials (RCTs), systematic reviews, and meta-analyses
- **Level II:** Observational studies
- **Level III:** Guidelines and narrative reviews
- **No level:** References that were not fully indexed by level at the time of the literature search


The authors provided this information as a supplement to their article.

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The Resource Center also searched for relevant guidelines from the American College of Obstetricians and Gynecologists, the US Preventive Services Task Force, the Royal College of Obstetricians and Gynaecologists, the European Society for Medical Oncology, the National Comprehensive Cancer Network® (NCCN®), the Society of Obstetricians and Gynaecologists of Canada, the Society of Gynecologic Oncology, the American College of Radiology, the National Institute for Health and Care Excellence, and the American Society for Reproductive Medicine (ASRM). A single investigator reviewed the titles and abstracts of all collected articles and guidelines. Selected manuscripts were then reviewed in full.

Inclusion criteria were major professional society or health service guidelines, systematic reviews, meta-analyses, RCTs, cohort studies, and case–control studies available in English and published between 2000 and 2021. Case reports, case series, and articles unavailable in English were excluded, as were articles from outside of countries designated very high in the United Nations Human Development Index.

Priority was given to systematic reviews and meta-analyses, and individual source studies were generally not reviewed separately unless they contained additional pertinent information not otherwise found in the review. Nonsystematic review articles were generally excluded except when high-quality studies could not be found for a specific topic.

**RESULTS**

The literature review returned 1,885 results. There were 112 level I studies reviewed (104 systematic reviews or meta-analyses and eight RCTs), 943 level II studies, and 171 level III studies. Another 659 papers were reviewed addressing risk (316 that did not meet the criteria for a higher level of evidence and 343 from PubMed that were not previously included).
The titles and abstracts for all level I studies were reviewed. If additional information was needed, the titles and abstracts for level II studies were reviewed.

Of the 112 level I studies, following review of the titles and abstract, 31 papers met criteria and were included. Another 21 level II studies were reviewed.

A total of 11 publications were reviewed from the American College of Obstetricians and Gynecologists and 31 from other professional organizations, including NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) and ASRM.

**What Lifestyle Factors are Risk Factors for Ovarian Cancer? How Strong Are These Risks?**

**Diet**

A systematic review and meta-analysis of 97 cohort studies found no significant association between risk of ovarian cancer and dietary intake.\(^1\) Subgroup analysis showed a significantly reduced ovarian cancer risk with diets that included green leafy vegetables (RR 0.91, 95% confidence interval [CI] 0.85–0.98), allium vegetables (RR 0.79, 95% CI 0.64–0.96), fiber (RR 0.89, 95% CI 0.81–0.98), and green tea (RR 0.61, 95% CI 0.49–0.76) (see Table 1). There was an increased risk of ovarian cancer with dietary intake of total fats (RR 1.10, 95% CI 1.02–1.18), saturated fats (RR 1.11, 95% CI 1.01–1.22), saturated fatty acids, cholesterol (RR 1.13, 95% CI 1.04–1.22), and retinol (RR 1.14, 95% CI 1.00–1.30).\(^1\) Intake of nonfood contaminants such as acrylamide (RR 1.18, 95% CI 1.02–1.37) and nitrate (RR 1.36, 95% CI 1.02–1.80) also significantly increased the risk of ovarian cancer.
### Table 1. Dietary Intake and Risk of Ovarian Cancer*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Studies</th>
<th>RR (95% CI)(^\dagger)</th>
<th>(p^\dagger)</th>
<th>(p^\ddagger)</th>
<th>(I^2) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fruits, Vegetables, and</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mushrooms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>20</td>
<td>0.92 (0.99–1.06)</td>
<td>0.707</td>
<td>0.798</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Fruits</strong></td>
<td>13</td>
<td>1.01 (0.96–1.07)</td>
<td>0.604</td>
<td>0.142</td>
<td>29.5</td>
</tr>
<tr>
<td><strong>Fruits and vegetables</strong></td>
<td>6</td>
<td>1.00 (0.93–1.07)</td>
<td>0.952</td>
<td>0.268</td>
<td>22.0</td>
</tr>
<tr>
<td><strong>Green leafy vegetables</strong></td>
<td>10</td>
<td>0.91 (0.85–0.98)</td>
<td>(0.009^{\ddagger})</td>
<td>0.115</td>
<td>35.5</td>
</tr>
<tr>
<td><strong>Allium vegetable</strong></td>
<td>3</td>
<td>0.79 (0.64–0.96)</td>
<td>(0.021)</td>
<td>0.996</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Meats and Eggs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>17</td>
<td>1.14 (0.96–1.35)</td>
<td>0.124</td>
<td>0.906</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Total meat</strong></td>
<td>8</td>
<td>1.07 (0.94–1.22)</td>
<td>0.316</td>
<td>0.041</td>
<td>47.2</td>
</tr>
<tr>
<td><strong>Eggs/eggs dishes</strong></td>
<td>9</td>
<td>1.12 (0.96–1.30)</td>
<td>0.140</td>
<td>0.231</td>
<td>23.8</td>
</tr>
<tr>
<td><strong>Dairy Products</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Total</strong></td>
<td>17</td>
<td>1.04 (0.95–1.13)</td>
<td>0.452</td>
<td>0.984</td>
<td>0.0</td>
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<tr>
<td><strong>Fats and Fatty Acids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>18</td>
<td>1.06 (0.98–1.14)</td>
<td>0.139</td>
<td>0.972</td>
<td>0.0</td>
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<th>Total fat</th>
<th>10</th>
<th>1.10 (1.02–1.18)</th>
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<th>0.435</th>
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<td>Animal fat</td>
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<td>0.059</td>
<td>0.050</td>
<td>46.7</td>
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<tr>
<td>Saturated fats</td>
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<td>1.11 (1.01–1.22)</td>
<td>0.023</td>
<td>0.380</td>
<td>6.6</td>
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<tr>
<td>Saturated fatty acids</td>
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<td>0.520</td>
<td>0.0</td>
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<tr>
<td>Cholesterol</td>
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<td>1.13 (1.04–1.22)</td>
<td>0.002</td>
<td>0.263</td>
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<table>
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<td>Total</td>
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<td>Wine</td>
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<td>Retinol</td>
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<td>Fiber</td>
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<tr>
<td>Total</td>
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<tr>
<td>Tea</td>
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<tr>
<td>Green tea</td>
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<tr>
<td>Coffee</td>
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<table>
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<th>Nonfood Contaminants</th>
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<tr>
<td>Total</td>
<td>14</td>
<td>1.06 (0.91–1.23)</td>
<td>0.474</td>
<td>0.719</td>
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<td>Acrylamide</td>
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<tr>
<td>Nitrate</td>
<td>3</td>
<td>1.36 (1.02–1.80)</td>
<td>0.034</td>
<td>0.001</td>
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</table>


RR, relative risk; CI, confidence interval

P, P value (probability)

Data marked in bold are statistically significant.

The Women’s Health Initiative Dietary Modification trial is the only RCT evaluating the association of dietary modification with cancer risk. In the study, 48,835 women were randomly assigned to either the dietary modification group (n = 19,541, 40%) or usual diet group (n = 29,294, 60%) and monitored for an average of 8.1 years. The goal of the intervention group was to reduce total fat intake to 20% of energy and to increase consumption of grains (>6 servings/day) and fruits and vegetables (>5 servings/day). Although no difference was found in the first 4 years, this study showed a statistically significant reduction in ovarian cancer risk among those in the dietary modification group in the last 4 years of follow-up (hazard ratio [HR] 0.60, 95% CI 0.38–0.96).

The National Institutes of Health–AARP cohort study assessed diet and health among older people via a mailed questionnaire. It identified 695 cases of ovarian cancer and found a significant positive association with ovarian cancer among women who consumed the highest amount of total fats (RR 1.28, 95% CI 1.01–1.63, P = .04). This study showed...
an increased risk of ovarian cancer with animal fat intake (RR 1.30, 95% CI 1.02–1.66). In contrast, the California Teacher cohort study did not show an association between total fat intake and risk of ovarian cancer (RR 0.85, 95% CI 0.58–1.24, P = .26).

A systematic review of prospective cohort studies to evaluate the role of diet in ovarian cancer risk showed a higher risk of ovarian cancer with total animal fat and dairy intake but no association with red meat, fiber, vitamin A, vitamin E, beta-carotene, or folate. Vegetables were associated with lower risk in one of three studies; fruit showed no association, although risk estimates were all greater than 1.0. Isoflavones and flavonoids were associated with modestly lower risk in two studies. Tea intake was associated with lower risk in one of two studies.

A meta-analysis of eight observational studies suggested an increased risk of ovarian cancer with high total fat intake (RR 1.24, 95% CI 1.07–1.43).

The Netherlands Cohort Study on Diet and Cancer, a prospective study, identified 280 cases of ovarian cancer and found no association with tea (RR 0.94, 95% CI 0.89–1.00, P = .12) or coffee (RR 1.04, 95% CI 0.97–1.12, P = .35) per cup per day. The same investigators performed a meta-analysis of case-control and cohort studies evaluating the association of coffee and tea intake with risk of ovarian cancer. This meta-analysis showed a decreased risk of ovarian cancer when the results were pooled for tea intake in the cohort group (RR 0.85, 95% CI 0.71–1.01, P = .002) but no association with coffee intake (RR 1.18, 95% CI 0.97–1.44, P = .13).

**Alcohol Use**

A comprehensive meta-analysis of 27 observational studies with a total of 16,554 epithelial ovarian cases did not show an association between alcohol intake and the risk of epithelial ovarian cancer (RR 1.0, 95% CI 0.95–1.05). A pooled analysis of 5,342 cases and 10,358 controls from the Ovarian Cancer Association Consortium also did not show an
association between total alcohol intake and ovarian cancer (>3 drinks/day compared to none; OR 0.92, 95% CI 0.76–1.10, \(P = .27\)).

In a population-based study looking at adult lifetime alcohol intake that categorized the type of alcohol rather than recent use, wine consumption was associated with a risk reduction (adjusted odds ratio [aOR] 0.67, 95% CI 0.50–0.88) relative to nondrinkers, but beer consumption was not. The reduced risk was stronger for those who drank red wine exclusively (aOR 0.44, 95% CI 0.19–0.92) compared with white wine drinkers (aOR 0.79, 95% CI 0.46–1.34). In their systematic review and meta-analysis of 97 cohort studies, Khodavandi and colleagues identified seven relevant studies and found no significant association between wine intake and ovarian cancer (see Table 1).

**Physical Activity**

In a meta-analysis of 34 studies looking at the association of physical activity, physical inactivity, and ovarian cancer risk, any physical activity, whether low (2–4 h/wk), medium (4–7 h/wk), or high (≥7 h/wk), was associated with a decrease in ovarian cancer compared with no physical activity (<2 h/wk). Compared with no physical activity, the risk decreased as follows:

- Low physical activity: 9% (RR 0.91, 95% CI 0.86–0.97, \(P < .05\))
- Medium physical activity: 9% (RR 0.91, 95% CI 0.87–0.96, \(P < .05\))
- High physical activity: 8% (RR 0.93, 95% CI 0.89–0.98, \(P < .05\))

In an evidence-based review, data from all case–control studies demonstrated risk reductions of at least 20% among women who are regularly active.
Physical inactivity was associated with an increased risk of ovarian cancer. A low amount of sitting time (≥3 h but <7 h) increased the risk of ovarian cancer by 1.14 times (95% CI 1.06–1.23, \( P < .05 \)) and a high amount of sitting time (≥7 h) increased the risk by 1.28 times (95% CI 1.13–1.46, \( P < .05 \)).\(^{11}\) These findings were supported by a pooled analysis of 8,309 ovarian cancer cases in which inactive women had a 34% increased risk of epithelial ovarian cancer (OR 1.34, 95% CI 1.14–1.57 \( P < .0001 \)).\(^{13}\)

**Smoking**

A meta-analysis found no association between smoking and the overall risk of ovarian cancer (RR 1.05, 95% CI 0.95–1.16, \( P > .01 \)).\(^{14}\) However, looking at tumor histology, current smokers had a higher risk than never-smokers for mucinous cancer (RR 1.78, 95% CI 1.52–2.07) and a decreased risk for clear cell (RR 0.77, 95% CI 0.65–0.93) and endometrioid cancers (RR 0.81, 95% CI 0.73–0.91). No association was noted between smoking and serous cancer (RR 1.05, 95% CI 0.94–1.17).

A systematic review found a significant doubling of risk of mucinous ovarian cancer among current smokers compared with never-smokers (RR 2.1, 95% CI 1.7–2.7), but no increased risk of serous (RR 1.0, 95% CI 0.8–1.2) or endometrioid (RR 0.8, 95% CI 0.6–1.1) cancers and a significant risk reduction for clear cell cancers (RR 0.6, 95% CI 0.3–0.9).\(^{15}\)

A pooled analysis of 21 case–control studies found that current cigarette smoking increased the risk of invasive mucinous (OR 1.31, 95% CI 1.03–1.65) and borderline mucinous ovarian tumors (OR 1.83, 95% CI 1.39–2.41), while former smoking increased the risk of borderline serous ovarian tumors (OR 1.30, 95% CI 1.12–1.50).\(^{16}\)

On the basis of six articles, NCCN Guidelines state that smoking has been associated with mucinous ovarian cancer but is also associated with a decreased risk of clear cell carcinoma.\(^{17}\)
**Talcum Powder Use**

A meta-analysis of talcum powder use found a statistically significant increased risk of ovarian cancer (RR 1.33, 95% CI 1.16–1.45) when 16 studies were pooled. However, there was no clear dose response, raising questions about the validity of the findings. Further sensitivity analysis showed that studies conducted in hospital settings did not show a relationship between the use of talcum and ovarian cancer risk (RR 1.19, 95% CI 0.99–1.41) compared with population-based studies (RR 1.38, 95% CI 1.25–1.52).

In another meta-analysis, the RR for ovarian cancer among those who had ever used talcum powder was 1.22 (95% CI 1.13–1.30). The RR for case–control studies was 1.26 (95% CI 1.17–1.35) and for cohort studies, 1.02 (95% CI 0.85–1.20, \( P_{\text{heterogeneity}} = .007 \)). Serous carcinoma was the only histologic type of ovarian cancer for which there was an association with talcum powder use (RR 1.24, 95% CI 1.15–1.34).

A third meta-analysis identified a positive association between perineal use of talcum powder and ovarian cancer (OR 1.28, 95% CI 1.20–1.37). This finding was supported by another meta-analysis that showed that any perineal talcum powder use was associated with an increased risk of ovarian cancer (OR 1.31, 95% CI 1.24–1.39).

The studies regarding the use of talcum powder and the risk of ovarian cancer are heterogenous. On the basis of seven studies, NCCN Guidelines state that environmental factors have not been conclusively associated with the development of ovarian cancer.

**What Hormonal Factors Are Risk Factors for Ovarian Cancer? How Strong Are These Risks?**

Several studies have shown that oral contraceptive use decreases the risk of ovarian cancer. In an analysis of six case–control studies, the reduction in ovarian cancer risk increased with longer duration of oral contraceptive use (OR 0.83, 95% CI 0.69–1.01 for <5 y; OR 0.42, 95% CI 0.30–0.59 for ≥5 y, compared to nonusers). This protective factor has
also been shown with contraceptive use in women at high risk for ovarian cancer. A meta-analysis of three case–control studies found a significantly reduced risk of ovarian cancer in $BRCA1$ and $BRCA2$ mutation carriers with any past use of combined oral contraceptives (OR 0.57, 95% CI 0.47–0.70; $P < .001$), and protection correlated significantly with duration of use (OR 0.95, 95% CI 0.93–0.97; $P < .001$). The use of intrauterine devices has been shown in a meta-analysis to decrease the risk of ovarian cancer (RR 0.66, 95% CI 0.52–0.84).  

In contrast, much of the published data regarding the use of menopausal hormone therapy show an increased risk of ovarian cancer. In a meta-analysis of 42 studies including 12,238 cases of ovarian cancer, estrogen-only hormone therapy was associated with a 1.28-fold increased risk (95% CI 1.18–1.40) of developing epithelial ovarian cancer, and estrogen-progestin hormone therapy was associated with a 1.11-fold increased risk (95% CI 1.02–1.21). The United Kingdom’s Million Women Study also saw an increased risk of ovarian cancer among those undergoing current hormone therapy (RR 1.20, 95% CI 1.09–1.32). This study also showed an increased risk with estrogen therapy use (RR 1.34, 95% CI 1.13–1.60) compared with estrogen-progestin therapy (RR 1.14, 95% CI 1.01–1.20). The average age of the participants studied was 57. According to the authors of the Million Women Study, the risk of ovarian cancer did not vary significantly according to the hormonal constituents, the mode of administration, or the type of hormone therapy regimen. A systematic review of the literature determined that ovarian cancer risk increased with estrogen therapy use (RR 1.22, 95% CI 1.18–1.27, $P < .001$); the risk was lower but still increased with estrogen-progestin therapy use (RR 1.10, 95% CI 1.04–1.16). In this systematic review, estrogen therapy use increased ovarian cancer risk in a duration-dependent manner.

Parity is associated with a decreased risk of ovarian cancer. In a population-based case–control study, parous women had a significant reduction in ovarian cancer risk (OR 0.4, 95% CI 0.3–0.6). Women with one birth had a 40% reduced risk, while the risk was reduced by 80% for women with five or more births. In another study, parous women had a
reduced risk for serous ovarian tumors (OR 0.44, 95% CI 0.26–0.75) and mucinous ovarian tumors (OR 0.63, 95% CI 0.34–1.19).33

Later age of menarche and earlier age of menopause have been shown to be associated with a decreased risk of ovarian cancer. In a case–control study, the OR for ovarian cancer was 0.8 (95% CI 0.6–1.0) for those reporting menarche at age 15 or older compared with those age 12 or younger.34 In contrast, women who reported menopause before age 45 had an OR of ovarian cancer of 0.6 (95% CI 0.5–0.9) compared with women who reported menopause at age 45 or older.34 In a cohort study in the Netherlands, the risk of ovarian cancer was reduced in relation to each year reduction in time between menarche and menopause (HR 0.98, 95% CI 0.95–1.00).35 The same study found a 3% reduction in ovarian cancer risk for each year that total menstrual lifespan was reduced (HR 0.97, 95% CI 0.95–0.99).35 In a systematic review, the cumulative duration of menstrual cycles was associated with an increased risk of ovarian cancer (<36 y vs ≤27 y: HR 1.57, 95% CI 1.16–2.13).36

Breastfeeding has been associated with a decreased risk of ovarian cancer.36–42 Although breastfeeding in general is associated with a decreased risk in the development of ovarian cancer, there has not been consistency in studies regarding the duration of breastfeeding that has been most protective. In a systematic review and meta-analysis of 15 studies on breastfeeding, categorized by duration (<6 months, 6–12 months, and >12 months), the protective effect of breastfeeding decreased after 6 months.41 The summary RR by duration were 0.79 (95% CI 0.72–0.87), 0.72 (95% CI 0.64–0.81), and 0.67 (95% CI 0.56–0.79), respectively.41 In a study of two prospective cohorts, breastfeeding for 18 months or more compared with never breastfeeding was associated with a significantly decreased risk of ovarian cancer (RR 0.66, 95% CI 0.46–0.96).37 In this study, the RR decreased by 2% for each month of breastfeeding (RR 0.98, per month, 95% CI 0.97–1.00).37
What Family Health History Factors Are Risk Factors for Ovarian Cancer? How Strong Are These Risks?

The risk of ovarian cancer has been shown to be increased in those with certain genetic mutations. At least 10% of epithelial ovarian cancers are caused by germline mutations in *BRCA1* and *BRCA2*.\(^43\) In a population-based study of 209 ovarian cancer cases, 15% resulted from *BRCA1* and *BRCA2* mutations.\(^44\) In a meta-analysis, the risk of ovarian cancer by age 70 was estimated to be 39% (95% CI 22%–51%) in women with *BRCA1* mutation and 11% (95% CI 4.1%–18%) in women with *BRCA2* mutation.\(^45\)

*BRIP1*, *RAD51C*, and *RAD51D* are other genetic mutations that have been associated with an increased risk of ovarian cancer. Mutations in these three genes, cumulatively, are estimated to be associated with 2% of ovarian cancer cases.\(^46\) In a meta-analysis of 29,400 ovarian cancer patients, the risk of ovarian cancer was significantly elevated for those with *BRIP1* (OR 4.94, 95% CI 4.07–6.00), *RAD51C* (OR 5.59, 95% CI 4.42–7.01), or *RAD51D* (OR 6.94, 95% CI 5.10–9.44).\(^46\)

For those with Lynch syndrome, the cumulative lifetime risk of ovarian cancer varies between 6% and 12%.\(^47\) In a systematic review, the most frequent mutations in women with Lynch syndrome who had ovarian cancer were *MLH1* (38%) and *MSH2* (47%).\(^47\) Other genetic mutations and the absolute risk of epithelial ovarian cancer are shown in Table 2.

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<th>Gene</th>
<th>Epithelial Ovarian Cancer Absolute Risk</th>
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<td><em>ATM</em></td>
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<tr>
<td><em>BRCA1</em></td>
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</tr>
<tr>
<td><em>BRCA2</em></td>
<td>13%–29%</td>
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Burke W, Barkley J, Barrows E, Brooks R, Gesci K, Huber-Keener K, et al. Executive Summary of the Ovarian Cancer Evidence Review Conference. Obstet Gynecol 2023;142. The authors provided this information as a supplement to their article. ©2023 The Authors.
<table>
<thead>
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<th>Gene</th>
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<tr>
<td>BRIP1</td>
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</tr>
<tr>
<td>MLH1, MSH2</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>MSH6</td>
<td>≤13%</td>
</tr>
<tr>
<td>PMS2</td>
<td>&lt;3%</td>
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<tr>
<td>EPCAM</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>PALB2</td>
<td>3%–5%</td>
</tr>
<tr>
<td>RAD51C</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>RAD51D</td>
<td>&gt;10%</td>
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No association with ovarian cancer has been established for the genetic mutations involving CDH1, CDKN2A, CHEK2, NF1, PTEN, STK11, and TP53.48

Family history of cancer has been shown to increase one’s risk of ovarian cancer. A study of children from mothers with breast or ovarian cancer found that, for daughters of women with breast cancer, the standardized morbidity ratio for being diagnosed with ovarian cancer before the age of 50 was 1.28 (95% CI 1.05–1.54).49 For daughters of women with ovarian cancer, the standardized morbidity ratio for ovarian cancer was 2.38 (95% CI 1.77–3.12). The risk was elevated if the mother’s cancer was diagnosed at a young age, the mother had multiple breast or ovarian cancer diagnoses, or...
there was a sister with breast or ovarian cancer. Importantly, this population-based study was published in 2000 and did not assess for genetic mutations such as \textit{BRCA1} or \textit{BRCA2}, which are strongly linked to the familial risk of developing ovarian cancer.

In a case–control study of 554 first-degree relatives of women with ovarian cancer, ovarian cancer in a first-degree relative was significantly associated with increased risk of ovarian cancer (OR 2.4, 95% CI 1.4–4.1).\textsuperscript{50} In this study, ovarian cancer in a first-degree relative appeared to be a stronger risk factor for early-onset (<50 y) ovarian cancer than late-onset (OR 5.3, 95% CI 2.0–14.1 vs. OR 1.8, 95% CI 1.0–3.4).

In a case–control study of 1,463 women (626 with a history of breast cancer and 548 with a history of ovarian cancer), women with a family history of breast or ovarian cancer or both had an OR of ovarian cancer of 2.2 (95% CI 1.3–3.8).\textsuperscript{51} The risk was higher when the proband was younger or when two or more relatives were affected.

\section*{What Prior Health History Factors Are Risk Factors for Ovarian Cancer? How Strong Are These Risks?}

Endometriosis has been shown to be a risk factor for ovarian cancer.\textsuperscript{52–55} In a meta-analysis using data from 13 ovarian cancer case–control studies, endometriosis was significantly associated with increased risk of clear cell carcinoma (OR 3.05, 95% CI 2.43–3.84), endometrioid invasive ovarian cancers (OR 2.04, 95% CI 1.67–2.48), and low-grade serous carcinoma (OR 2.11, 95% CI 1.39–3.20).\textsuperscript{54} These findings are supported by the results of another meta-analysis in which endometriosis was more associated with endometrioid carcinoma (RR 1.759, 95% CI 1.551–1.995) and clear cell carcinoma (RR 2.606, 95% CI 2.225–4.053) histology compared to non-endometriosis-associated ovarian cancer cases.\textsuperscript{53} However, in this meta-analysis, serous carcinoma was noted to be less frequent with endometriosis (RR 0.733, 95% CI 0.617–0.871). There was no association between endometriosis and the risk of mucinous carcinoma (RR 0.805, 95% CI 0.584–1.109).\textsuperscript{53} Another meta-analysis of 12 case–control studies specifically evaluating epithelial ovarian cancer and endometriosis also found a significant increased risk with endometriosis (OR 1.42, 95% CI 1.28–1.57).\textsuperscript{55}


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Tubal ligation has been shown to decrease the risk of ovarian cancer. In a meta-analysis of 13 studies, having a tubal ligation reduced the risk of epithelial ovarian cancer by 34% (RR 0.66, 95% CI 0.60–0.73). This finding was supported by another meta-analysis of 25 cases in which tubal ligation was noted to significantly decrease the risk of epithelial ovarian cancer (OR 0.70, 95% CI 0.60–0.78).

Obesity has been shown to be associated with many cancers. A meta-analysis found a nonlinear positive association between ovarian cancer risk, body mass index (BMI), and weight, with a significant association between ovarian cancer and a BMI of 28 or greater. In another review by Foong and Bolton, 14 studies found a statistically significant positive association between ovarian cancer risk and higher BMI, 26 studies did not find a significant association, and three found a negative association. In a systematic review and meta-analysis of obesity and ovarian cancer, 24 of 28 studies reported a positive association between obesity and ovarian cancer. Ten of those studies were noted to be statistically significant. The pooled effect estimate for adult obesity was 1.3 (95% CI 1.1–1.5) and for overweight was 1.2 (95% CI 1.0–1.3).

Many studies have evaluated the risk of ovarian cancer associated with fertility and the use of assisted medical technology. In a 2020 meta-analysis including nine prospective cohort studies and 10,383 patients with ovarian cancer, the RR of the association between infertility and ovarian cancer was 1.51 (95% CI 1.35–1.69), with low heterogeneity. A systematic review of six cohort studies and seven case–control studies reviewing the association of ovulation induction medication and ovarian cancer did not find an association between fertility drugs and epithelial cancer. It did identify an association between borderline tumors and fertility drugs, but this finding was not consistent across the studies reviewed.

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A Cochrane review of 37 studies, including a total of 4,684,724 women, did not find enough strong evidence to suggest a potentially higher risk of ovarian cancer in women treated with fertility drugs.69

In a meta-analysis of three cohort studies and seven case–control studies, the risk of ovarian cancer did not appear to be increased in patients with infertility who were treated with assisted medication compared with patients with infertility who were not treated. Case–control and cohort data showed subjects who underwent assisted reproductive technology with infertility medications had a significantly elevated risk for ovarian cancer compared with general population controls (1.52, 95% CI 1.18–1.97).66 Among infertile patients who did or did not undergo treatment, the risk for ovarian cancer was not elevated among the treated group (OR 0.99, 95% CI 0.67–1.45). The cohort data suggest a lower incidence of ovarian cancer in infertile patients who used assisted reproductive technology compared with infertile patients who did not undergo treatment (OR 0.67, 95% CI 0.32–1.41).

A population-based case–control study of 902 cases of ovarian cancer found no association among women who reported ever using fertility medications (OR 0.93, 95% CI 0.65–1.35) or women seeking medical services for their infertility (OR 0.87, 95% CI 0.54–1.40).67

The ASRM states that there is no significant increased risk of ovarian cancer following use of fertility drugs.70 The ASRM does state that some studies show a small increased risk of borderline tumors, but there is not sufficient evidence to recommend against the use of fertility medications to avoid borderline ovarian tumors.70

DISCUSSION

In this review, several risk factors, such as lifestyle, were reviewed to determine their association with ovarian cancer. A woman's reproductive history has been shown to contribute to her lifetime risk of ovarian cancer. Factors that decrease ovulation should decrease the risk of ovarian cancer. Several studies have shown that oral contraceptive use significantly

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decreases the risk of ovarian cancer. The duration of use of oral contraceptives has also been shown to be a protective factor for ovarian cancer. Other factors, such as parity, later age of menarche, earlier age of menopause, and breastfeeding have all been shown to significantly decrease the risk of ovarian cancer. The use of postmenopausal hormonal therapy has been shown to increase the risk of ovarian cancer.

Many studies have reviewed the association between specific diets and ovarian cancer. Currently, the data are inconsistent, likely because of the heterogeneity of the studies conducted and reviewed. The Women’s Health Initiative study suggests that long-term adoption of a low-fat diet may reduce the risk of ovarian cancer in postmenopausal women. A systematic review and meta-analysis suggests a potential decreased risk of ovarian cancer with the intake of green leafy vegetables, green tea, fiber, and allium vegetables but a potential increase in ovarian cancer risk with increased dietary intake of total fats, saturated fats, saturated fatty acids, nitrate, acrylamide, cholesterol, and retinol. There was also a heterogeneity of data regarding various diets and the risk of ovarian cancer. There is not a specific diet that consistently increases or decreases the risk of ovarian cancer. Although there is no direct evidence that dietary modification affects risk of ovarian cancer, the data align with general recommendations for a healthy diet.

Although there are increasing data to suggest an association of alcohol intake with breast cancer, the current data from this literature review did not show an increased risk of ovarian cancer associated with alcohol use. There is heterogeneity in the various types of alcohol studied in the literature, and more data would be needed to assess the ovarian cancer risk association with each type of alcohol.

The evidence reviewed was consistent in supporting that physical activity decreased the risk of ovarian cancer (the more physical activity, the lower the risk), while inactivity was associated with increased risk of ovarian cancer. The data regarding obesity and the risk of ovarian cancer are inconsistent, possibly because of the association of obesity with other confounding risk factors and the inability to adjust for those risk factors. Other potential causes for this
inconsistency have been attributed to the fact that many of the studies relied on self-reported weight, which could have been underestimated in overweight and obese women. Another potential limitation is that obesity in these studies was defined according to BMI, but some may state that this is not the best way to define obesity.

Some evidence suggests that smoking increases the risk of mucinous ovarian cancer and decreases the risk of clear cell carcinoma. This situation has been difficult to study given the relatively small number of cases and the many subtypes of ovarian cancer.

There is heterogeneity in the studies regarding the use of talcum powder and ovarian cancer, which may contribute to the inconsistent data. In one meta-analysis there was a difference in findings between the population-based subjects and hospital-based patients. It is therefore thought that the positive association between talcum powder use and ovarian cancer risk in population-based studies may be the result of selection bias as well other potential confounders. Another meta-analysis found that the association between ovarian cancer and talcum powder use varied depending on the type of study. Therefore, there are inconsistent data to determine whether the use of talcum is associated with ovarian cancer.

The data in this review did not show that fertility medication increased the risk of ovarian cancer. There may be an association between the use of fertility medication and borderline ovarian tumors, but the data have been inconsistent. Infertility can be a risk factor for ovarian cancer given that these patients tend to have low parity and are less likely to be using contraception because of the desire for pregnancy. Thus, these women are at increased risk for ovarian cancer in comparison to the general population. Many of the studies were retrospective and did not include detailed information regarding specific types, dosages, or the number of cycles of medications used, which could potentially affect one’s risk of ovarian cancer. There were also limited studies on the use of fertility medications, specifically in patients with genetic predisposition to ovarian cancer, such as those with BRCA1 or BRCA2 mutations. Large, prospective cohort studies are needed.
needed in this area. The findings of this review are consistent with the ASRM guideline, which states that there is no significant increased risk of ovarian cancer following the use of fertility drugs, but there potentially may be an increased risk of borderline ovarian tumors.

There have been consistent data suggesting an association between endometriosis and invasive ovarian carcinoma. There appears to be a stronger association of endometriosis with clear cell carcinoma. Most of the cases in the meta-analyses came from case–control studies. Among limitations noted was a concern for recall bias in self-reported endometriosis cases. Selection bias could have also been a factor in these studies as well, because the cases were often identified in the hospital setting. Some studies only included moderate or severe cases of endometriosis, and others might not have accounted for confounding risk factors, such as infertility or the duration of use of oral contraceptives, which could contribute to the association with ovarian cancer. However, the data reviewed found a consistent association between endometriosis and clear cell carcinoma.

Tubal ligation has consistently been shown in the data to decrease the risk of ovarian cancer. A potential bias in these studies is that woman seeking tubal ligation likely have other protective factors, such as high parity or use of oral contraception. Screening bias may result from the selective removal of suspicious ovaries during tubal ligation. In this review, tubal ligation was not specifically defined in terms of the various methods used. In the meta-analyses reviewed, there was no distinction of the type of tubal ligation noted to determine whether salpingectomy was associated with ovarian cancer.

This literature review did not find any data on transgender or nonbinary people, which represents a research gap.

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RESEARCH GAPS

- More data are needed to assess the risk of ovarian cancer associated with each type of alcohol.
- Large, prospective cohort studies are needed about the use of fertility medications, specifically in patients with genetic predisposition to ovarian cancer, such as those with BRCA1 or BRCA2 mutations.
- No data were available regarding risk factors for ovarian cancer among transgender or nonbinary people.

REFERENCES


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INTRODUCTION

This document focuses on interventions that might be effective for reducing the risk of ovarian cancer in women at average or high risk. Appendix 3, Risk Factors for Ovarian Cancer, summarizes the data on risk for ovarian cancer related to lifestyle factors, hormonal factors, prior health history, and family history. To address risk reduction and prevention, a literature search was carried out based on the question, “Which interventions are effective at reducing ovarian cancer in average-risk and high-risk women?” The PICO format was used to direct the literature review:

\[
P = \text{patient, problem, or population; I = intervention; C = comparison, control, or comparator; O = outcome(s)}
\]

- **P**: Adults with ovaries (eg, women and transgender men)
- **I**: Preventive strategy (lifestyle modifications, hormonal contraception [broken out by combined hormonal contraception, intrauterine device, or IUD, types, progestin only, when possible], salpingectomy, or oophorectomy)
- **C**: One preventive strategy vs another preventive strategy, regular care, or no strategy
- **O**: Relative risk (RR) or odds ratio (OR) of ovarian cancer, incidence of ovarian cancer
METHODS

The American College of Obstetrics and Gynecologists’ (ACOG’s) Resource Center conducted a literature search using Cochrane, MEDLINE, and PubMed databases for all relevant references involving prevention and risk reduction for ovarian cancer among individuals with ovaries. The literature search was supplemented by examining pertinent bibliographies of included studies.

Inclusion criteria were major professional society or health service guidelines, systematic reviews, meta-analyses, randomized control trials (RCTs), and observational studies published in the year 2000 or later. Only articles available in English were included. Case reports, case series, articles not available in English, and abstract-only articles were excluded.

Priority was given to systematic reviews and meta-analyses. Nonsystematic review articles were generally excluded unless there was a lack of high-quality studies on the specific topic.

A single investigator reviewed the title and abstracts of all identified articles. The full text of those articles that met eligibility criteria were then reviewed by the same investigator. A secondary reviewer reviewed the findings and made suggestions or additions.

RESULTS

The literature search found four guidelines from professional organizations specific to reducing the risk of ovarian cancer in women at high or average risk. The literature search identified 583 publications, 55 of which addressed the proposed question. After title and abstract review, 475 references were excluded primarily because they did not answer the question or were older studies that were included in systematic reviews. Cost-effectiveness and decision analysis studies...
were not included. Studies on diet, smoking, alcohol, obesity, childbearing, postmenopausal hormone therapy, infertility, and use of infertility drugs were also excluded because they were determined to be potential risk factors that are not necessarily modifiable for the purpose of preventing ovarian cancer and are covered in Appendix 3, Risk Factors for Ovarian Cancer. An additional 53 papers were excluded after full-text review for similar reasons: wrong populations, wrong outcome (patient decision making, nonclinical measure), or wrong intervention (screening).

Risk-Reducing Surgery

Risk-Reducing Bilateral Salpingo-Oophorectomy (rrBSO)

A meta-analysis from 2007 of 10 population-based studies reported the mean cumulative ovarian cancer risk for BRCA1 and BRCA2 mutation carriers to be 40% (95% confidence interval [CI] 35%–46%) and 18% (95% CI 13%–23%), respectively. A 2009 meta-analysis of six studies (case–control and cohort) with 2,840 subjects showed an 80% reduction in the incidence of ovarian cancer after rrBSO in BRCA1 and BRCA2 carriers (95% CI 0.12–0.39).

A 2014 meta-analysis also showed risk reduction with rrBSO. In this review, three prospective studies (representing 9,192 patients) were included in the final analysis, and the authors noted reduced ovarian cancer risk (hazard ratio [HR] 0.19, 95% CI 0.13–0.27)] and all-cause mortality (HR 0.32, 95% CI 0.27–0.38) in patients undergoing rrBSO compared to controls. Additionally, they evaluated outcomes by BRCA subtype, identifying two studies including 4,310 patients with a mean follow-up of 4.8 years. Ovarian cancer risk was reduced in the BRCA1 subgroup (HR 0.20, 95% CI 0.12–0.32), whereas there was no significant difference among BRCA2 patients (HR 0.21, 95% CI 0.02–1.91, P = .22). For women who choose not to undergo rrBSO, penetrance estimates by age 70 years are 48.3% (95% CI 38.8%–57.9%) for BRCA1 carriers and 20.0% (95% CI 13.3%–29.0%) for BRCA2 carriers. In BRCA carriers who do not undergo rrBSO, risk of ovarian cancer peaks at age 55–60 years for BRCA1 carriers and later for BRCA2 carriers.
Safety of the procedure was evaluated in several studies. One study from 2002 that prospectively followed women who chose to undergo rrBSO or surveillance reported on complications. Four of the 98 women who chose rrBSO had complications that included wound infection (one patient), bladder perforation (one patient), small bowel obstruction (one patient), and uterine perforation from the manipulator (one patient). In 2017, a study that prospectively monitored 85 women undergoing rrBSO found no severe complications and only four mild complications that included fever (three patients) and ileus (one patient).

Concern about the effects of estrogen deprivation and quality of life after rrBSO have been explored. A retrospective study from 2003 questioned 59 women who underwent rrBSO using five different standardized symptom scales at a mean of 2 years following surgery. Symptoms of estrogen deprivation were reported, including vaginal dryness (35.2%) and dyspareunia (27.7%), and were the most significant predictors of satisfaction with surgery. Another study from 2005 that included 845 high-risk women compared those who had undergone rrBSO (44%) and those who had not (56%). No significant difference was noted in quality of life between the groups or compared to the general population. Women in the rrBSO group noted worse sexual pleasure \( (P < .5) \) and more discomfort during sex \( (P < .5) \) but had similar levels of sexual activity. A 2009 prospective study compared 75 high-risk women who underwent either rrBSO (38 subjects) or serial surveillance (37 subjects) to assess quality of life, sexual functioning, and depressive symptoms at baseline and at 1, 6, and 12 months. At baseline and by the 6-month assessment, the groups showed no significant difference in quality of life or depressive symptoms. Hot flashes \( (P < .03) \) and vaginal dryness \( (P < .01) \) were the only significant difference in symptoms between the two groups.

A systematic review conducted by the Gynecologic Surgeons Systematic Review Group to compare the long-term risks associated with salpingo-oophorectomy at the time of benign hysterectomy identified 26 studies that compared ovarian conservation to removal in women at average risk who underwent hysterectomy for benign indications. Three of the studies (totaling 82,404 patients) reported on the incidence of ovarian cancer. The prevalence of ovarian cancer was
higher when ovaries were left in situ (0.14%–0.7% compared with 0.02%–0.04% among those with bilateral salpingo-oophorectomy [BSO]). Cardiovascular outcomes were evaluated in six studies that included 142,120 patients and showed that coronary heart disease (HR 1.26, 95% CI 1.04–1.54) and cardiovascular death were higher among women with BSO (HR 1.84, 95% CI 1.27–2.68), especially in women younger than 45 years who were not treated with estrogen. Three studies evaluated all-cause mortality, which was found to be higher in women who were younger than 45 years at the time of BSO and who did not receive estrogen therapy (HR 1.41, 95% CI 1.04–1.92).

The Society of Gynecologic Oncology (SGO) recommends that rrBSO be performed between the ages of 35 and 40 years for women at increased genetic risk of ovarian cancer.\textsuperscript{10} It states that the timing can be individualized according to the earliest age of onset in the family and personal choices. Preservation of ovaries is advisable for average-risk women.\textsuperscript{10} The National Comprehensive Cancer Network (NCCN) recommends risk-reducing salpingo-oophorectomy, typically between ages 35 and 40 years and on completion of childbearing in women with \textit{BRCA1}. Because ovarian cancer onset in patients with \textit{BRCA2} is an average of 8–10 years later than in patients with \textit{BRCA1}, it is reasonable to delay risk-reducing salpingo-oophorectomy for management of ovarian cancer risk until age 40–45 years in patients with \textit{BRCA2} unless age at diagnosis in the family warrants earlier consideration of prophylactic surgery.\textsuperscript{11} ACOG also recommends rrBSO between the ages of 35 and 40 for \textit{BRCA1} carriers, whereas women with \textit{BRCA2} may consider delaying until age 40–45 years because of the later onset of ovarian cancer.\textsuperscript{12}

According to NCCN, there is insufficient evidence to recommend a specific age at which rrBSO should be considered in carriers of moderately penetrant genetic mutations associated with ovarian cancer (eg, \textit{ATM}, \textit{NBN}, and \textit{PALB2}).\textsuperscript{11} Cancer risk management intervention may be recommended when a carrier’s absolute risk exceeds that of the average-risk population (1%–2% for ovarian cancer). As a result, rrBSO should not be considered until the woman’s lifetime risk of developing ovarian cancer exceeds a threshold of 3%. Lifetime risk for carriers of \textit{BRIP1} (12%), \textit{RAD51C} (11%), and \textit{RAD51D} (13%) exceeds this threshold, and for these individuals, NCCN states that rrBSO should be considered between


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the ages of 45 and 50 or earlier if warranted based on family history. Women with Lynch syndrome are at increased risk of endometrial and ovarian cancers (up to 60% and 24%, respectively), and, for these individuals, NCCN states that total hysterectomy and BSO should be considered when childbearing is completed.11

When completing a rrBSO, ACOG recommends that all tissue from the ovaries and fallopian tubes be removed.12 The ovarian vessels should be isolated and ligated approximately 2 cm proximal to the end of identifiable ovarian tissue, and the fallopian tube should be divided at its insertion into the uterine cornu and the ovary removed at the utero-ovarian ligament as close to the uterus as possible. When performing a laparoscopic procedure, the specimen should be placed in an endoscopic bag before removal from the abdomen. Pelvic washings should be collected, and thorough visualization of the peritoneal surfaces should be achieved with biopsies taken of any abnormal-appearing tissue. Complete, serial sectioning of the ovaries and fallopian tubes is necessary, with microscopic examination for occult cancer.12

**Tubal Ligation and Salpingectomy**

In a 2011 study, Cibula et al identified 16 case–control, three retrospective cohort, and two prospective cohort studies regarding the risk of ovarian cancer after tubal ligation.13 In the 13 studies that were included in their meta-analysis, the authors found that previous tubal ligation in women at average risk for ovarian cancer was associated with a 34% overall risk reduction (RR 0.66, 95% CI 0.60–0.73). A higher reduction in risk was found for endometrioid invasive cancers (RR 0.40, 95% CI 0.30–0.53) compared to serous cancers (RR 0.73, 95% CI 0.63–0.85). The New England Case–Control study compared 2,265 patients with ovarian cancer to 2,333 controls.14 Tubal ligation was associated with a lower risk of epithelial ovarian cancer (OR 0.82, 95% CI 0.68–0.97), and this inverse association was stronger for women who had undergone the procedure at the time of last delivery (OR 0.60, 95% CI 0.42–0.84) rather than later (OR 0.93, 95% CI 0.75–1.15).
A meta-analysis from 2016 that evaluated the risk of ovarian cancer after bilateral salpingectomy included three studies, one retrospective cohort study, and two population-based case–control studies. Over the combined study period, 29 of the 3,509 patients who underwent bilateral salpingectomy developed ovarian cancer, compared with 44,006 of the 5,655,702 who did not have salpingectomy (OR 0.51, 95% CI 0.35–0.75). A 2017 systematic review by Darelius et al included 11 studies evaluating salpingectomy outcomes. Although none of the studies evaluated ovarian cancer risk after opportunistic salpingectomy at the time of hysterectomy, two retrospective studies reported a decreased ovarian cancer risk after indicated salpingectomy (adjusted HR 0.65, 95% CI 0.52–0.81). The authors also reported a longer operative time (16 minutes) but no significant difference in complication rates or hospital stay and no difference in endocrine function when salpingectomy was performed at the time of hysterectomy (surrogate measures used included hormones [luteinizing hormone, follicle-stimulating hormone, estradiol, and anti-Müllerian hormone] and ultrasound measurements [antral follicle count, mean ovarian volume, pulsatile index, resistance index, and systole/diastole ratio]).

A study using Nationwide Inpatient Sample data on women who had hysterectomy with bilateral salpingectomy found no increased risk for blood transfusion (adjusted OR [aOR] 0.95, 95% CI 0.86–1.05), postoperative complications (aOR 0.97, 95% CI 0.88–1.07), postoperative infections (aOR 1.26, 95% CI 0.90–1.78), or fevers (aOR 1.33, 95% CI 1.00–1.77) compared with women who had hysterectomy alone. A retrospective cohort study of 49,275 women found no differences in rates of minor complications 2 weeks after surgery among women who underwent opportunistic salpingectomy. Our review found no studies demonstrating a lasting, significant change in laboratory markers of ovarian reserve after bilateral tubal ligation or bilateral salpingectomy, whether performed at the time of hysterectomy or for sterilization alone. A 2019 Swedish registry-based study reported a significant increase in menopausal symptoms 1 year following salpingectomy with hysterectomy (n = 1,433) compared with hysterectomy alone (n = 3,473) (RR 1.33, 95% CI 1.04–1.69).
ACOG states that salpingectomy should be considered at the time of hysterectomy, in lieu of tubal ligation, and at the time of other pelvic surgery performed after completion of childbearing.\(^\text{20}\) Salpingectomy can be safely performed at the time of vaginal hysterectomy, and plans to perform an opportunistic salpingectomy should not alter the intended route of hysterectomy. Additionally, it also appears that postpartum salpingectomy is appropriate and safe at the time of cesarean delivery. SGO states that salpingectomy can be considered in average-risk women undergoing hysterectomy, other pelvic surgery, or sterilization after the completion of childbearing.\(^\text{10}\) SGO also recommends that, after salpingectomy, the fimbria of the fallopian tube in women who are not at high risk be embedded and microscopically examined. A review of guidelines on opportunistic salpingectomy from member societies of the International Federation of Gynecology and Obstetrics found that 13 societies commented on the procedure. None of the societies had negative comments; nine supported opportunistic salpingectomy, and the other four were ambivalent.\(^\text{21}\)

ACOG recommends that when performing a salpingectomy, the interstitial portions of the tube do not need to be removed, but the tube should be removed completely from the uterotubal junction to the fimbriated end.\(^\text{20}\) Any remaining fimbrial attachments on the ovary should be cauterized or removed. If it is not possible to perform a complete salpingectomy, then removing as much of the fallopian tubes as possible, excluding the interstitial portion, may still be valuable. Complete salpingectomy is preferred over fimbriectomy because precursors to fallopian tube cancer (or ovarian cancer) can be found throughout the fallopian tube.\(^\text{20}\)

**Salpingectomy with Delayed Oophorectomy**

In a recent, nonrandomized, prospective pilot study, 43 \textit{BRCA1} and \textit{BRCA2} carriers, ages 30–47 years, were asked to decide between screening, rrBSO, and salpingectomy with delayed oophorectomy.\(^\text{22}\) In the latter group, \textit{BRCA1} carriers were assigned to undergo delayed oophorectomy by age 40 years and \textit{BRCA2} carriers by age 45 years. Among all the participants, 19 (44%) chose salpingectomy with delayed oophorectomy, 12 (28%) chose rrBSO, and 12 (28%) chose screening. No intraoperative complications occurred and no occult cancer was found in the group that selected screening.


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salpingectomy with delayed oophorectomy. Only one serous tubal intraepithelial carcinoma was found in the rrBSO group. Overall, patients were satisfied with their procedure choice and had a reduction in cancer worry and anxiety.

SGO states, “Bilateral salpingectomy can be considered at the completion of childbearing in women at increased genetic risk of ovarian cancer who do not agree to rrBSO.”¹⁰ SGO emphasizes that salpingectomy is not a substitute for oophorectomy, which should still be performed as soon as the woman is willing to accept menopause, preferably by the age of 40 years. Women delaying or refusing rrBSO will reduce or not receive breast cancer risk reduction or the potential therapeutic benefit in those with a personal history of breast cancer. NCCN states that salpingectomy alone in high-risk patients is not the standard of care but that clinical trials are ongoing.¹¹ Additionally, NCCN comments that in premenopausal \textit{BRCA1} and \textit{BRCA2} carriers, oophorectomy can reduce the risk of breast cancer by 50%.

\textbf{Surgical Treatment of Endometriosis}

In a 2012 study, pooled data from 13 case–control studies from the Ovarian Cancer Association Consortium were evaluated for the association between endometriosis and ovarian cancer.²³ A total of 13,226 controls and 7,911 women with invasive ovarian cancer were included in this analysis. Self-reported endometriosis was associated with a significantly increased risk of clear cell (OR 3.05, 95% CI 2.43–3.84) and endometrioid invasive ovarian cancers (OR 2.04, 95% CI 1.67–2.48). No association was noted between endometriosis and risk of mucinous (OR 1.02, 95% CI 0.69–1.50) or high-grade serous invasive ovarian cancer (OR 1.03, 95% CI 0.97–1.32).

Another case–control study that included 1,571 women diagnosed with invasive ovarian cancer and 2,100 population-based controls found that having a history of endometriosis strongly increased the risk for endometrioid and clear cell tumors (OR 2.41, 95% CI 1.78–3.26).²⁴ In a population-based case–control study that included 496 cases and 908 controls, a history of endometriosis was strongly associated with an increased risk of type I tumors (OR 2.96, 95% CI 1.54–5.67), but not type II tumors.²⁵ Type I tumors arise predominantly from the ovary, including lower-grade

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endometrioid adenocarcinomas, clear cell carcinomas, mucinous adenocarcinomas, and low-grade serous carcinomas. Type II tumors are those that are less clearly of ovarian origin; however, many of these have well-described carcinogenic precursors in the distal fallopian tube.

One Swedish nested case–control study among women with a first-time hospital discharge diagnosis of endometriosis observed a reduction in risk of developing ovarian cancer after surgical removal of endometriosis (aOR 0.30, 95% CI 0.12–0.74) and unilateral salpingo-oophorectomy (aOR 0.19, 95% CI 0.08–0.46) as treatment.26 A population-based longitudinal record-linkage study of 837,942 women across a 27-year period found that among women ever diagnosed with endometriosis, hysterectomy was associated with substantially decreased ovarian cancer risk (HR 0.17, 95% CI 0.12–0.24 overall).27

Chemoprevention

**Oral Contraceptive Use**

A recent systematic review by Huber et al that included four meta-analyses, one systematic review, one case–control study, and one retrospective cohort study looked at the association between ovarian cancer and oral contraceptive use in BRCA mutation carriers.28 They found that all the studies reported a risk reduction for the oral contraceptive users, and several also found that the longer the duration of use, the more the risk decreased. In a meta-analysis based on 18 studies and 1,503 ovarian cancer cases, oral contraceptive use was associated with a significantly reduced risk of ovarian cancer (summarized RR 0.50, 95% CI 0.33–0.75), with an additional risk reduction of 36% for each additional 10 years of oral contraceptive use (summarized RR 0.64, 95% CI 0.53–0.78).29

A retrospective study from 2021 noted that for BRCA1 carriers who use oral contraceptives, duration of use proved to be the most prominent protective factor for risk reduction (compared with <5 years, 5–9 years’ use had an HR of 0.67 [95% CI 0.40–1.12], and >10 years’ use had an HR of 0.37 [95% CI 0.19–0.73]).30 This inverse association between duration of
use and ovarian cancer risk persisted for more than 15 years after discontinuing use (duration of ≥10 years’ use, for
BRCA1 patients <15 years since last use, the HR was 0.24 [95% CI 0.14–0.43] and for BRCA1 patients >15 years since last
use, HR was 0.56 [95% CI 0.18–0.59]). One case–control study of 232 cases and 232 matched controls found that among
BRCA1 carriers, the combination of tubal ligation and past use of an oral contraceptive was associated with an OR of
ovarian cancer of 0.28 (95% CI 0.15–0.52).31

The meta-analysis by Huber also reported on breast cancer risk.28 It noted that some studies reported a risk elevation,
while others did not find an association between oral contraceptive use and breast cancer in BRCA mutation carriers. In
other studies, the association was limited to early-onset breast cancer or associated with young age at first start of oral
contraceptives.29 Formulations of oral contraceptives used before 1975 were associated with a significant increased risk
of breast cancer (summarized RR 1.47, 95% CI 1.06–2.04), but no evidence of significant risk with more recent
formulations was found (summarized RR 1.17, 95% CI 0.74–1.86)(Schrijver, 2021).30

In women at average risk, a 2013 meta-analysis of 24 case–control and cohort studies noted a significant reduction in
ovarian cancer incidence in ever-users compared with never-users of oral contraception (OR 0.73, 95% CI 0.66–0.81),
with a 50% reduction noted after 10 or more years of use.32 Lifetime reduction in ovarian cancer attributable to the use
of oral contraceptives was approximately 0.54%, with a number needed to treat of approximately 185. In 2008, a
reanalysis of data from 45 epidemiologic studies including 23,257 women with ovarian cancer and 87,303 controls
showed that for every 5 years of oral contraceptive use, the overall RR of ovarian cancer decreased by 20% (95% CI
18%–23%).33 A Canadian population-based case–control study that included 854 ovarian cancer cases and 2,139 controls
noted a 9% risk reduction (95% CI 0.86–0.96) per year for use before a first full-term pregnancy, but no risk reduction for
use after.34
A study looking at data from Los Angeles County, California, that included 1,632 cases and 2,340 controls found that oral contraceptive use for 5 years before age 35 was associated with greater protection compared with 5 years of use after age 35 (34% vs 14%, $P < .019$). Each 5 years of use was associated with a 28% lower risk of ovarian cancer ($P < .001$). The protective effect of oral contraceptive use continued even after stopping use, with similar risk reduction noted in women who stopped oral contraceptive use more than 20 years before compared with those who stopped less than 10 years before (OR 0.81, 95% CI 0.040–1.66). An observational study of 256,661 women in the United Kingdom noted a time-independent risk reduction for oral contraceptive users (HR 0.62, 95% CI 0.52–0.75) that was statistically significant up to 35 years after last use. Risk reduction did not differ between the use of current low-dose pills and the high-dose formulations used in the past (OR 0.5, 95% CI 0.3–0.7). Additionally, in a meta-analysis using data from four large trials, oral contraceptive use was associated with a greater decreased risk of rapidly fatal ovarian cancer (5-year increase in RR was 0.69, 95% CI 0.58–0.82) versus less aggressive disease (RR 0.81, 95% CI 0.74–0.89; difference between RRs $P = .002$) (Poole, 2013).

SGO states that oral contraceptives reduce the risk of ovarian cancer for average-risk women and BRCA1 and BRCA2 mutation carriers. It states that women with BRCA1 or BRCA2 mutations should consider taking oral contraceptives to reduce their ovarian cancer risk and that appropriate counseling about side effects and contraindications will allow each patient to weigh the risks and benefits. ACOG states that it is appropriate for women with mutations in BRCA1 or BRCA2 to use oral contraceptives if indicated, and their use for cancer prophylaxis is reasonable.

**Other Contraceptives**

In 2019, a meta-analysis by Wheeler et al reviewed nine case–control and two cohort studies on IUD use and ovarian cancer risk among women of reproductive age. Ever-use of IUDs was associated with a 32% decrease in the incidence of ovarian cancer (summary OR 0.68, 95% CI 0.62–0.75). This benefit was seen across multiple different IUD types (copper, levonorgestrel-releasing, and stainless steel).
studies (one of which was included in the Wheeler review) evaluating the levonorgestrel intrauterine system (LNG-IUS) did not show a lower risk of ovarian cancer relative to the never-use of LNG-IUS, with an estimated OR of 0.66 (95% CI 0.41–1.08).41

In one prospective cohort study of 1,879,227 women from Denmark, those who currently or recently used any hormonal contraception and those reporting former use of any hormonal contraception had a reduced risk of ovarian cancer (RR 0.58, 95% CI 0.49–0.68, and RR 0.77, 95% CI 0.66–0.91, respectively) compared with never-users.42 Use of progestogen-only products was not associated with ovarian cancer risk.42

**Other Agents for Chemoprevention**

Results from three separate meta-analyses of nonsteroidal anti-inflammatory drugs showed mixed results. In the most recent analysis (published in 2016), Zhang et al included eight cohort studies and 15 case–control studies and noted risk reduction associated with aspirin use (RR 0.89, 95% CI 0.83–0.96).43 A pooled analysis from 12 population-based studies with a total sample size of over 10,000 subjects found 20% to 34% risk reduction with daily low-dose (<100 mg) aspirin use (OR 0.91, 95% CI 0.84–0.99), with the reduced risk found to be strongest among daily aspirin users (OR 0.80, 95% CI 0.67–0.96). Results were similar but not statistically significant for nonaspirin nonsteroidal anti-inflammatory drugs (OR 0.90, 95% CI 0.77–1.05), and there was no association with acetaminophen.44

A systematic review from 2010 that included 10 ecologic studies, six case–control studies, and four cohort studies examining the relationship of vitamin D to ovarian cancer found no consistent or strong evidence to support that vitamin D exposures, whether measured through circulating levels, dietary or supplement intake, or proxy measures, are associated with a reduced risk for ovarian cancer incidence or mortality.45 Additionally, a meta-analysis from 2011 on circulating vitamin D levels and ovarian cancer incidence that included 10 case–control and prospective cohort studies noted that vitamin D use did not demonstrate a statistically significant risk reduction (RR 0.83, 95% CI 0.63–1.08).46 A
A single RCT on fenretinide, a synthetic vitamin A analog, showed a lower incidence of ovarian cancer in women with prior breast cancer over a 5-year period (0 vs 6 cases, \( P = .03 \)); however, this protective effect ceased after discontinuing the study agent.\(^\text{47}\) A Canadian cohort study found that relatively high dietary intake of folate (HR 0.39, 95% CI 0.19–0.80) and vitamin B6 (HR 0.49, 95% CI 0.24–0.98) were inversely associated with risk of ovarian cancer.\(^\text{48}\)

**Lifestyle Factors**

**Breastfeeding**

A 2021 systematic review and meta-analysis of five studies, including one cohort study and four case–control studies, investigated breastfeeding and the risk of ovarian cancer in **BRCA1** and **BRCA2** mutation carriers.\(^\text{49}\) Of the 14,601 **BRCA1** and **BRCA2** mutation carriers, the overall pooled OR of ever having breastfed in patients who had ovarian cancer was 0.767 (95% CI 0.688–0.856) for patients with **BRCA1** mutation and 0.817 (95% CI 0.650–1.028) for patients with **BRCA2** mutation. Breastfeeding for more than 1 year acted as a protective factor in both **BRCA1** (OR 0.787, 95% CI 0.682–0.907) and **BRCA2** (OR 0.567, 95% CI 0.400–0.802) mutation carriers. A matched case–control study from 2020 concluded similarly that breastfeeding had a protective effect.\(^\text{50}\) Compared with **BRCA** carriers who never breastfed, breastfeeding for 7 or more months was associated with a 32% reduction in risk (OR 0.68, 95% CI 0.57–0.81). This study additionally noted that the combination of breastfeeding and oral contraceptive use was strongly protective (OR 0.47, 95% CI 0.37–0.58).

The effect of breastfeeding on ovarian cancer incidence in average-risk women was evaluated by Koushik et al in 2017.\(^\text{25}\) In their study, a history of breastfeeding did not demonstrate a decreased overall risk of epithelial ovarian cancer but did have a protective effect against type I invasive cancers (OR 0.45, 95% CI 0.23–0.88). A large meta-analysis of five cohort and 35 case–control studies reported a 24% reduction in ovarian cancer risk with breastfeeding (95% CI 0.69–0.83), and a longer duration of breastfeeding was associated with decreased risk of ovarian cancer.\(^\text{51}\)
DISCUSSION

Our review did not find any RCTs that support any specific risk-reduction strategy for either high-risk or average-risk women. Additionally, there were no studies on the transgender population.

Surgical Prevention

Risk-reducing BSO is the mainstay of ovarian cancer prevention in BRCA1 and BRCA2 carriers and is recommended in this population by ACOG, NCCN, and SGO.\(^{10-12}\) Our review noted studies with different effects of risk-reducing procedures between BRCA1 and BRCA2 patients. However, studies of BRCA2 patients were likely underpowered to detect a difference given the small numbers and the overall decreased incidence of ovarian cancer in BRCA2 carriers compared to BRCA1 carriers. We found no studies to suggest that the risk of primary peritoneal carcinoma is reduced with rrBSO. In women at average risk, BSO offers the advantage of effectively eliminating the risk of ovarian cancer and reoperation but can be detrimental to other aspects of health, especially among women younger than age 45 years.

Our review did not find any prospective studies that estimated ovarian cancer risk reduction with opportunistic salpingectomy alone, either among high-risk women or those at baseline population risk of developing the disease. Existing retrospective data support that bilateral salpingectomy is at least comparable, if not superior, to bilateral tubal ligation as prophylaxis against ovarian cancer and should be considered in average-risk women undergoing sterilization.\(^{13,14}\) When comparing operative risks between bilateral salpingectomy and bilateral tubal ligation, the available studies show no difference in complication rates and only a minimal increase in operative time when performing bilateral salpingectomy during an interval or postpartum sterilization. While we found no prospective studies or major professional society recommendations, based on these data, many surgeons perform opportunistic salpingectomy at the time of other gynecologic procedures, such as hysterectomy.
Importantly, our review did not identify data to support salpingectomy alone in high-risk women. Anecdotal evidence of an increase in the number of high-risk women being offered salpingectomy with delayed oophorectomy indicates that there is a potentially false perception of decreased risk in these patients after salpingectomy, which may ultimately decrease the odds of their timely return for ovary removal.\textsuperscript{52} Multiple studies are underway to evaluate the risks and benefits of salpingectomy with delayed oophorectomy in women at high risk for ovarian cancer.\textsuperscript{53,54} Two independent trials are currently recruiting BRCA mutation carriers with the goal of evaluating the impact of salpingectomy (with delayed oophorectomy) on noncancer endpoints, including safety, acceptability, menopausal symptoms, and quality of life.\textsuperscript{53,54} Preliminary results suggest that both women choosing salpingectomy with delayed oophorectomy and women undergoing rrBSO have significant improvements in cancer-related distress following surgery, with women choosing rrBSO experiencing greater improvements in distress.\textsuperscript{55}

Limited studies suggest that surgical treatment of endometriosis may have an ancillary benefit of reducing risk of developing ovarian cancer. Our review found only two studies of risk reduction after surgical treatment in endometriosis patients. We found no major society guidance.

**Chemoprevention**

Our review found multiple studies and systematic reviews that consistently showed decreased ovarian cancer risk with hormonal contraceptive use in average-risk and high-risk women, which supports oral contraceptive use for prevention. Studies on other types of contraception demonstrated mixed results for ovarian cancer risk. Studies on IUDs demonstrated conflicting data, as did progesterone-only systemic treatment. None of the studies showed an increased risk for ovarian cancer. Aspirin use also has been demonstrated to show a slight risk reduction; however, no guidelines recommend aspirin use for prevention of ovarian cancer. No other agents have demonstrated risk reduction or have recommendations for use.
Lifestyle Factors

Our review demonstrates that breastfeeding appears to have a protective effect for both average-risk and high-risk women. Women are routinely encouraged to breastfeed; however, there are no national guidelines or recommendations for breastfeeding as prevention against ovarian cancer.

RESEARCH GAPS

The following research gaps were identified:

- There were no prospective RCTs of any preventive measures in high-risk or average-risk women.
- There were no prospective data about opportunistic salpingectomy at the time of bilateral tubal ligation or other pelvic surgery.
- There were no data on transgender patients.
- There were no data on salpingectomy with delayed oophorectomy in BRCA1 and BRCA2 patients.

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INTRODUCTION

This document examines the evidence for screening for ovarian cancer in average-risk and high-risk populations. High-risk subgroups are identified that can potentially benefit from screening. The literature review was directed by the questions listed. The PICO format was used to direct the literature review:

\[ P = \text{patient, problem, or population}; \ I = \text{intervention}; \ C = \text{comparison, control, or comparator}; \ O = \text{outcome(s)} \]

1. What is the evidence against screening asymptomatic average-risk women?

\[ P: \text{Adult patients with ovaries, average-risk, without symptoms} \]
\[ I: \text{Ovarian cancer screening (transvaginal ultrasonography, serum markers)} \]
\[ C: \text{Screening vs no screening} \]
\[ O: \text{Relative risk (RR) or odds ratio (OR) of ovarian cancer, incidence of ovarian cancer, stage at diagnosis, survival rate, false-positive screen, or need for surgery} \]

2. Are there high-risk subgroups that benefit from screening? How can high-risk women be identified?

\[ P: \text{Adult patients with ovaries with Cowden syndrome, Lynch syndrome, BRCA mutation, family history of unexplained ovarian cancer, polycystic ovarian syndrome, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, or family history of ovary-related cancers} \]

The authors provided this information as a supplement to their article.
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I: Assessment of family history, genetic testing

C: One assessment measure vs another vs no assessment or usual care

O: RR or OR of ovarian cancer, incidence, or stage at diagnosis

3. How should screening be performed in high-risk subgroups?

P: Adult patients with ovaries with BRCA mutations, Cowden syndrome, Lynch syndrome, family history of unexplained ovarian cancer, Li-Fraumeni syndrome, or Peutz-Jeghers syndrome

I: Ovarian cancer screening (transvaginal or pelvic ultrasonography, serum markers)

C: Screening vs no screening, one screening method vs another

O: RR or OR of ovarian cancer, incidence, stage at diagnosis, survival rate, false-positive rate, or need for surgery

METHODS

The American College of Obstetricians and Gynecologists’ (ACOG’s) Resource Center searched the Cochrane, MEDLINE through Ovid, and PubMed databases for all relevant references. There was also a review of relevant guidelines published by the American Society of Clinical Oncology, ACOG, the American College of Radiology, the American Society for Reproductive Medicine, the European Society for Medical Oncology, the National Comprehensive Cancer Network (NCCN), the National Institute for Health and Care Excellence, the Royal College of Obstetricians and Gynaecologists, the Society of Gynecologic Oncology, the Society of Obstetricians and Gynaecologists of Canada, and the US Preventive Services Task Force (USPSTF).

Inclusion criteria were major professional society or health service guidelines, systematic reviews, meta-analyses, randomized control trials (RCTs), and observational studies published in the year 2000 or later. Only articles available in English were included. Case reports, case series, articles not available in English, and abstract-only articles were
Results were categorized according to the following levels of evidence:

- **Level I:** RCTs, systematic reviews, and meta-analyses
- **Level II:** Observational studies
- **Level III:** Guidelines and narrative reviews
- **No level:** References that were not fully indexed by level at the time of the literature search

**RESULTS**

The literature review returned 1,051 results. There were 197 level I studies, 275 level II studies, and 215 level III results. An additional 364 articles were reviewed addressing risk (262 that did not meet higher level of evidence and 102 papers from PubMed that were not identified in the original search). After title and abstract review, 58 papers met criteria and were included in this literature review, including guidelines from a number of major professional societies and health services; the remaining results did not meet criteria, were duplicates, or were included in the larger reviews. Of the literature included, most articles were found to have a high level of evidence or were relevant to the discussion of the need for additional evidence in determining the level of risk. Two articles were included that did not meet original search criteria but provided additional support where evidence was lacking.

**What Is the Evidence Against Screening Asymptomatic Average-Risk Women?**

Although the prevalence of ovarian cancer in the United States is relatively low, mortality from epithelial ovarian cancer is relatively high, mostly due to the later stage of diagnosis.¹ The majority of high-grade ovarian cancer (95%) is found with regional or distant spread (stage II–IV).² Although ovarian cancer mortality is decreasing, according to National
Cancer Institute Surveillance, Epidemiology, and End Results data, the 5-year survival rates from 2004 to 2014 for epithelial ovarian cancer were 67.7% (95% confidence interval [CI] 65.4–69.8) for regional stages and 32.1% (95% CI 31.1–33.0) for distant stages. When high-grade serous ovarian cancer is found at an early stage, 5-year survival is much higher, with rates of 84% (95% CI 80.4–87.0). Clear cell ovarian carcinoma and mucinous carcinoma have poor outcomes similar to high-grade serous ovarian cancer at higher stages in terms of mortality, while all stages of low-grade serous and endometrioid carcinomas have more favorable outcomes.

The difference in survival becomes important when discussing ovarian cancer screening and the ability to detect early stages of ovarian cancer. Unfortunately, ovarian cancer symptoms are nonspecific and common, which is likely the reason for the higher stage at diagnosis. The lack of specificity in ovarian cancer symptoms has led to a push to evaluate whether ovarian cancer screening of the general population is effective.

**Methods of Screening in Asymptomatic Average-Risk Women**

The most common methods proposed for ovarian cancer screening include transvaginal ultrasonography, bimanual palpation, and serum tumor markers. Transvaginal ultrasonography is used to identify structural changes to the ovary. Bimanual palpation is an integral part of routine pelvic examinations and, therefore, has been proposed as a screening modality for ovarian cancer. However, the utility of bimanual palpation to identify high-risk ovarian pathology has been questioned. The most common tumor marker used in ovarian cancer screening is cancer antigen (CA) 125, which is known to be elevated in the majority of women with advanced-stage, high-grade serous ovarian cancer. Algorithms using transvaginal ultrasonography and trends in tumor markers along with patient-specific information have been developed in an attempt to increase sensitivity and specificity.

The Risk of Ovarian Cancer Algorithm (ROCA) was first described by Menon et al in 2005. The model estimates risk of ovarian cancer based on age and change in serum CA 125, which is expected to rise with the development of ovarian
cancer and stay flat in controls who do not develop ovarian cancer. This algorithm then gives screening recommendations based on the calculated risk; for example, ultrasonography would be recommended for significant CA 125 increases, while repeat CA 125 assessment can be performed for intermediate risk. The algorithm was validated in an RCT of 13,582 women age 50 or older; ROCA had a specificity for epithelial ovarian cancer on screening of 99.8% (95% CI 99.7–99.9) and a positive predictive value of 19% (95% CI 4.1–45.6). ROCA has been used in the prospective United Kingdom Familial Ovarian Cancer Screening Study in addition to a large-scale RCT in the United Kingdom. It has also been used in the United States to evaluate data from the US Cancer Genetics Network ROCA study and the screening arm of the Gynecologic Oncology Group study of high-risk women. Another algorithm, the parametric empirical Bayes model, has been used to interpret serial CA 125 values and performed similarly to ROCA in an examination of the UK data sets. Other serum markers, circulating tumor cells, and algorithms have been suggested for screening for ovarian cancer, but this review did not find any high-level evidence for their validity in average-risk women.

**RCTs of Ovarian Cancer Screening in Asymptomatic Average-Risk Women**

Several large-scale RCTs have been performed evaluating ovarian cancer screening with transvaginal ultrasonography, serum tumor markers, or bimanual palpation with a variety of endpoints (eg, mortality, quality of life, cost, and morbidity). The Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS), published in 2008, monitored 82,487 postmenopausal women in Japan from 1985 to 1999, with follow-up ending in 2002. This study used yearly transvaginal ultrasonography and CA 125 evaluation. The average follow-up was 9.2 years. Subjects with a CA 125 value of 35 units/mL or a complex ovarian cyst greater than 4 cm were offered surgical diagnosis. The study found equal rates of ovarian cancer by histology and stage. The proportion of stage I ovarian cancer was higher in the screened group (63%) than in the control group (38%) but did not reach statistical significance \( P = .2285 \), as only 27 cancers were found in the screened group.
The Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial published in 2011 examined 154,900 postmenopausal subjects ages 55–74 years in the United States for up to 13 years. This study included both average- and high-risk patients; 17% had a family history of ovarian cancer. Screening was performed on 78,216 of the participants with annual serum CA 125 assessment (greater than 35 units/mL was considered abnormal) for a total of 6 years and annual transvaginal ultrasonography for the first 4 years of screening; in total, the patients had a median of 12.4 years of follow-up. Additionally, this trial also included bimanual ovarian palpation for the first 4 years, and no cancers were identified solely on the basis of palpation; the only two cancers found also showed increases in CA 125 or a mass on transvaginal ultrasonography or both. Further evaluation of the data examined the risk of ovarian malignancy with abnormal screening results. High-risk criteria (CA 125 increase to >45 units/mL, increase in cyst size to ≥6 cm with normal CA 125, or both) revealed a positive predictive value of 29% (95% CI 28.3%–30.3%), 13.3% (95% CI 10.5%–18.0%), and 42.9% (95% CI 40.0%–46.0%) in subsequent rounds of screening. Overall, the sensitivity for detection of ovarian cancer using high-risk criteria was 85.3%, specificity was 95.6%, positive predictive value was 29.6%, and negative predictive value was 99.7%.

ROCA was applied to the data from the PLCO trial to model whether the algorithm would have identified more ovarian cancer cases earlier. The findings suggest that using ROCA would have led to earlier diagnosis in 32% of cases, but did not reach statistical mortality benefit (RR 0.90, 95% CI 0.69 to 1.17). A more recent analysis published in 2016 added up to 6 more years of posttrial follow-up, for a median of 14.7 years, with no changes in the lack of mortality benefit of screening. Temkin et al analyzed histopathology data from the PLCO trial and came to the conclusion that only 15% of type II ovarian tumors were detected by screening at stage I or II; overall, 74% of ovarian cancers were type II, indicating that screening did not find these more aggressive cancers at an earlier stage. False-positive results were found in 3,285 women at the time of surgery, when no ovarian cancer was identified, and the rate of serious complications from surgery was 15%, indicating that surgery was not benign.
The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) monitored 202,638 postmenopausal women (ages 50–74 years) for 3–7 years. The prospective cohort trial included three randomized arms: control group with no screening, a group with annual transvaginal ultrasonography, and a group with annual CA 125 assessment with subsequent CA 125 repeat evaluation or transvaginal ultrasonography if increases in CA 125 occurred. Using ultrasonography for screening, only 26.1% (6/23) of women with type II epithelial ovarian cancer were diagnosed with early-stage (I or II) disease. Long-term study results were reported in 2016 after 11.1 years and included 101,299 women in the control group, 50,624 women in the multimodal screening group (ultrasonography plus ROCA), and 50,623 women in the ultrasonography-only group. These data suggested evidence of a diagnosis stage shift secondary to screening, with a higher proportion of early-stage cancers found in the multimodal group (40%) than the ultrasonography-only group (24%). However, ovarian cancer mortality reduction did not achieve statistical significance.

The UKCTOCS had a lower rate of complications from surgery, averaging 3.1% to 3.5%, and a total of 2,122 false-positive screens as determined by surgical intervention. A critique of the study is that the screening arm contained more nonepithelial and borderline cancer types that progress slowly and would not contribute to mortality.

A 2021 update to the UKCTOCS by Menon et al included long-term mortality effects from screening with ROCA and transvaginal ultrasonography with a median of 16.3 years of follow-up. Although this study reported a 47.2% increase (95% CI 19.7–81.1) in stage I and 24.5% decrease (95% CI −41.8 to −2.0) in stage IV disease in the ROCA-plus- ultrasonography group, the overall incidence of stage III or IV disease was only 10.2% lower (95% CI −21.3 to 2.4). Despite this possible change in stage of diagnosis, overall, there was no significant reduction in ovarian cancer deaths among those screened by ROCA plus ultrasonography (P = .58) or ultrasonography alone (P = .36) compared with those who had no screening. This study highlighted the importance of long-term data and using ovarian cancer mortality as the primary outcome for these screening trials.
A smaller RCT, the UK pilot study of 21,935 postmenopausal women with 7 years of follow-up, was performed prior to the UKCTOCS to assess feasibility.\textsuperscript{24} The UK pilot study compared a control group with a screening group that underwent annual CA 125 evaluation. If CA 125 levels were greater than 30 units/mL, pelvic ultrasonography was performed and surgery offered for those with ovarian volume greater than 8.8 mL. This study showed a positive predictive value of 20.7% using screening and no statistical difference in the number of deaths from ovarian cancer between the control and screened groups.\textsuperscript{24}

These RCTs have been included in several systematic reviews and meta-analyses. The most recent 2018 systematic review was conducted by USPSTF for its updated publication on screening for ovarian cancer and included results from the UKCTOCS, the UK pilot study, and the PLCO trial.\textsuperscript{22} USPSTF did not include information from the SCSOCS trial out of Japan because of the lack of mortality data and the significantly lower prevalence of ovarian cancer (0.31/1,000) than expected in the US population.\textsuperscript{22}

Following its review, USPSTF maintained its recommendation against routine screening of average-risk women. The systematic review revealed no benefit for ovarian cancer mortality with screening. It found that the screened group in the PLCO trial compared to control groups had a RR of mortality of 1.18 (95% CI 0.82–1.71), while the UKCTOCS revealed hazard ratios (HRs) of 0.91 (95% CI 0.76–1.09) for the ultrasonography-screened group and 0.89 (95% CI 0.74–1.08) for the CA 125-screened group. USPSTF also found that only 1% of patients in the UKCTOCS who did not have cancer received surgical intervention on the basis of CA 125 assessment using ROCA, and in both trials, 3.2% of patients who did not have cancer had surgery on the basis of ultrasonography findings.\textsuperscript{22}

A 2018 study by Marchetti et al conducted a meta-analysis of the data from three of these RCTs of postmenopausal, asymptomatic women: SCOCS 2007 data, PLCO 2011 data, and UKCTOCS 2015 data.\textsuperscript{25} While the meta-analysis showed a trend toward earlier stage of diagnosis with ovarian cancer screening versus unscreened controls (RR 1.30, 95% CI 1.14–
1.49), it did not show a benefit of screening for disease-specific mortality (RR 0.96, 95% CI 0.85–1.10). It did show an increase in ovarian cancer diagnosis when the multimodal approach of CA 125 assessment with follow-up by ultrasonography was performed (RR 1.39, 95% CI 1.21–1.60). The study did not include the ROCA data from the UKCTOCS.25

A 2013 meta-analysis by Reade et al of older and smaller studies included 10 RCTs of asymptomatic women from 1979 to 2012 and showed no reduction in all-cause mortality with screening (RR 1.0, 95% CI 0.96–1.06) or ovarian cancer-specific mortality (RR 1.08, 95% CI 0.84–1.38).26 Additionally, the risk of advanced-stage (III or IV) ovarian cancer was not different between screened and unscreened groups (RR at stages III–IV 0.86, 95% CI 0.68–1.11). Surgery after a positive screen was not considered benign, as 6% of women experienced surgical complications (95% CI 1%–11%).26 This study suggests that ovarian cancer screening does not improve mortality or stage of ovarian cancer diagnosis in asymptomatic women and that surgical interventions have the potential for harm.

Professional Guidelines and Recommendations for Ovarian Cancer Screening in Average-Risk Women

We reviewed ovarian cancer screening guidelines and recommendations for average-risk women from ACOG, the American College of Radiology, the Society of Gynecologic Oncology, and USPSTF.22, 27-29 All of these groups stated that there was no current high-level evidence for the benefit of ovarian cancer screening in women at average risk. Therefore, none of these groups recommend ovarian cancer screening in asymptomatic average-risk women.

Are There High-Risk Subgroups that Benefit from Screening? How Can High-Risk Women Be Identified?

Traditionally, women with a high risk for ovarian cancer were identified when they reported a family history of ovarian cancer.30 It was also known that women who had family histories of other cancers, such as breast cancer, may be at risk for ovarian cancer. Approximately 13% to 15% of ovarian cancers in North America occur in patients with a pathogenic mutation in BRCA1 or BRCA2.31 With the advent of hereditary cancer genetic panel testing, women with family histories...
of other cancers can be identified if they test positive for a specific hereditary cancer predisposition syndrome or pathogenic variant in a gene that increases their risk of ovarian cancer. NCCN gives specific ranges of risk of developing ovarian cancer with pathogenic mutations in specific genes and updates these findings at least annually. Currently, NCCN lists **BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, MSH6, RAD51C, and RAD51D** as genes connoting high risk (>5% risk) for ovarian cancer, with more moderate risk for mutations in **ATM, PMS2, and PALB2**. NCCN also discusses the qualitative risks of sex cord-stromal and Sertoli-Leydig tumors with Peutz-Jeghers syndrome (**STK11**), mucinous epithelial ovarian cancer with Li-Fraumeni syndrome (**TP53**), and Sertoli-Leydig tumors with mutations in **DICER1**. NCCN states that there is no established increased risk of ovarian cancer with Cowden syndrome (**PTEN**). (See also Appendix 3, Risk Factors for Ovarian Cancer.)

We did not find specific studies on whether assessment of ovarian cancer risk and subsequent screening affected ovarian cancer stage or mortality. Only one systematic review stated that there was likely a moderate benefit to risk assessment. The USPSTF systematic review of risk assessment for **BRCA**-related cancer did not find any direct studies evaluating the effectiveness of risk assessment and genetic testing on **BRCA**-related cancer incidence, overall mortality, or disease-specific mortality; however, it did find indirect evidence of a moderate benefit of risk assessment in that identification of increased risk led to increased uptake in preventive and early detection measures that has been shown to improve outcome.

A small, prospective cohort study identified 419 women with **BRCA1** or **BRCA2** mutations who were evaluated in a Dutch high-risk clinic from 1999 to 2013 and studied them to see the impact on uptake of risk-reducing salpingo-oophorectomy (RRSO) when the clinic stopped offering ovarian cancer screening. Ovarian cancer screening had previously been offered to women at age 35 via annual gynecologic examination, CA 125 assessment, and transvaginal ultrasonography until October 2009. For women who received their DNA mutation results after screening was no longer offered, there was a shorter time interval to RRSO with a HR of 2.48 (95% CI 1.81–3.39). More women opted for RRSO within the
recommended ages when screening was not offered (95% vs 81%). The authors postulated that counseling for risk-management options may have differed and led to greater patient awareness of the ineffectiveness of ovarian cancer screening.34

**Professional Guidelines and Recommendations for Identifying High-Risk Women**

ACOG has several Practice Bulletins and Committee Opinions regarding the identification of high-risk women. “Family History as a Risk Assessment Tool” (ACOG Committee Opinion no. 478) counsels on the importance of using a pedigree or questionnaires to determine potential risks about family history of cancers while gathering information on the exact diagnosis, age of onset, and severity of disease.35 Specific findings in a pedigree that may indicate a higher likelihood of hereditary ovarian cancer include a known genetic condition in the family, ethnicity with a predisposition for certain hereditary disorders (such as in the Ashkenazi Jewish population), consanguinity, multiple affected family members with the same or related cancers, earlier-than-expected age of onset of disease, diagnosis in less-often-affected sex (such as with male breast cancer), multifocal occurrence in paired organs, and disease in the absence of risk factors or after prevention.35 “Cascade Testing: Testing Women for Known Hereditary Genetic Mutations Associated with Cancer” (ACOG Committee Opinion no. 727) recommends cascade genetic testing when family members test positive for a known hereditary genetic mutation.36 “Hereditary Cancer Syndromes and Risk Assessment” (ACOG Committee Opinion no. 793) discusses hereditary breast and ovarian cancer (BRCA1, BRCA2), Lynch syndrome (EPCAM, MLH1, MSH2, MSH6, PMS2), and Peutz-Jeghers syndrome (STK11) in terms of risks of different types of ovarian cancer.37 Additionally, ACOG has Practice Bulletins on hereditary breast and ovarian cancer syndrome and Lynch syndrome that specify how to identify women at higher risk for ovarian cancer associated with these syndromes.38,39

The most up-to-date recommendations for the assessment of women at high risk for ovarian cancer can be found in NCCN’s guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, which are updated at least annually.32 NCCN gives updated recommendations for genetic counseling based on family and personal histories.
along with the recommended screening for women found to be at high risk for ovarian cancer. NCCN reports that while high-level evidence is lacking, clinicians can consider, at their discretion, transvaginal ultrasonography and serum CA 125 evaluation for ovarian cancer screening for patients starting at ages 30–35 years, especially in women who have elected not to undergo a RRSO.32

The National Institute for Health and Care Excellence recommends genetic counseling for anyone with a family history of ovarian cancer and recommends a risk assessment for patients with breast cancer in first- or second-degree relatives.40 The Royal College of Obstetricians and Gynaecologists also gives guidance about who should be referred for genetic counseling and potential screening for genetic cancer syndromes that is similar to that of the other societies.41 The Society of Obstetricians and Gynaecologists of Canada recommends genetic counseling and does not recommend screening for high-risk patients at this time because of insufficient evidence.42 The 2017 American College of Radiology Appropriateness Criteria for Ovarian Cancer propose that there may be benefit to screening high-risk women for ovarian cancer.28

How Should Screening Be Performed in High-Risk Subgroups?

**RCTs of Ovarian Cancer Screening in Asymptomatic High-Risk Women**

Understandably, relatively few RCTs of ovarian cancer screening in high-risk women exist because RRSO is recommended for a considerable number of high-risk patients. Only two studies involving data from a large RCT were found in the literature search. A 2006 secondary analysis of the PLCO trial in ovarian cancer screening in women with a family history of breast or ovarian cancer studied 28,460 asymptomatic women who had annual transvaginal ultrasonography and serum CA 125 evaluation.43 Women were considered to be at average-risk if they had no relatives with breast cancer, moderate risk with one relative with breast cancer diagnosed after age 50, and high risk if they had a family member with breast cancer diagnosed before age 50, two relatives with breast cancer, or any relative with ovarian cancer. All groups had similar rates of abnormal screening results (4.8%–5.0%), and the positive predictive value

Burke W, Barkley J, Barrows E, Brooks R, Gesci K, Huber-Keener K, et al. Executive Summary of the Ovarian Cancer Evidence Review Conference. Obstet Gynecol 2023;142. The authors provided this information as a supplement to their article. ©2023 The Authors.
of abnormal screening results was 0.7% in average-risk, 1.3% in moderate-risk, and 1.6% in high-risk groups, none of which were statistically significant.\textsuperscript{43}

An additional analysis of the PLCO data in 2016 by Lai et al examined a subgroup of 22,355 women who reported a first-degree relative with breast or ovarian cancer.\textsuperscript{44} They found no significant difference in overall or disease-specific mortality. However, the 48 patients in the screening arm diagnosed with ovarian cancer did experience improved survival compared with the usual care arm, with a RR of 0.66 (95% CI 0.47–0.93).\textsuperscript{44} The authors hypothesized that the study was not powered to fully evaluate mortality, as only 48 patients in the screened group and 44 patients in the unscreened group, respectively, were found to have ovarian cancer.

Although there have been small pilot studies on the use of other tumor markers in high-risk ovarian cancer screening, there are no current large-scale data on the benefits of these other tumor markers. A small RCT pilot study was performed with 1,172 high-risk women ages 20–85 years, including women with known mutations in \textit{BRCA1}, \textit{BRCA2}, or \textit{TP53}, women with Lynch syndrome germline mutations, and women who met the 2013 NCCN criteria for genetic testing for hereditary breast and ovarian cancer.\textsuperscript{45} These women underwent semiannual screening with either CA 125 assessment followed by serum marker human epididymis protein 4 (HE4) assessment for any significant increase in CA 125 or CA 125 plus HE4 assessment. Significant increases were determined by the parametric empirical Bayes algorithm, which incorporates personal characteristics, such as age, ethnicity, and smoking, that can affect the tumor markers. Transvaginal ultrasonography was performed if there was a significant increase in either tumor marker. Only six surgeries were performed, and two ovarian malignancies were found, so the authors determined both arms combined had a positive predictive value of 33% (95% CI 4%–78%). When the authors examined intent to treat (37 women recommended for surgical consultation) rather than just the women who chose surgery, they found a positive predictive value of 14.3% in the group that had serial tumor marker assessment (95% CI 0.4%–57.9%) and 20% in the group that
had both markers assessed at the same time (95% CI 0.5%–71.6%), for a combined positive predictive value of 16.7% (95% CI 2.1%–48.4%).

Additional Studies on Ovarian Cancer Screening in Asymptomatic High-Risk Women

An important study not included above is the University of Kentucky Ovarian Cancer Screening Trial, which began in 1987 and included asymptomatic postmenopausal women ages 50 and older in addition to higher-risk women who were 25 or older with a family history of ovarian cancer. In this study, 23.2% of women were in the high-risk category as a result of family history. The trial is limited in that it was not randomized, but was instead a cohort comparison study design. Data from the trial, which included 37,000 women from 1987 to 2011, were published in 2011 after 5.7 years of follow-up. The screening group received annual ultrasound screening and repeat ultrasonography in 4–6 weeks when abnormal results were found; if the repeat ultrasonography was abnormal, CA 125 levels were assessed. Screened patients who went on to be diagnosed with ovarian cancer were then compared with unscreened women diagnosed with ovarian cancer who were identified through university or statewide databases. The trial originally reported a 5-year survival rate for women diagnosed with epithelial ovarian cancer detected by screening plus interval cancers of 74.8% ± 6.6% vs unscreened women diagnosed with ovarian cancer (53.7% ± 2.3%) with \( P < .001 \).

A 2018 updated publication from the University of Kentucky study reported on stage of detection and long-term survival of screening-detected ovarian cancer patients, with a mean age of ovarian cancer at 64.5 years. It found that 70% of screen-detected cancers were stage I or II, compared with 27% in observed controls. The 10-year survival rate for screening-detected epithelial ovarian cancer patients was 68% ± 7%, compared with 31% ± 2% for unscreened women treated with similar protocols at the same institution. The study design has been criticized for having no control group with a mixed-risk population of women and a higher rate of epithelial ovarian cancer than in the general population. Additionally, the study does not mention the specific histologies of the epithelial ovarian cancers. There were no
significant differences in the incidence of malignant tumors between groups, which was unexpected given the large proportion of women in the screening group who were considered to be at high risk.

Several other studies have examined transvaginal ultrasonography and CA 125 screening in high-risk patients. The Modena Study Group published a nonrandomized prospective cohort study from Italy in 2017 examining the effectiveness of transvaginal ultrasonography and CA 125 screening in 661 women at risk for ovarian cancer, including those with a family history or known BRCA1, BRCA2, TP53, MLH1, or MSH2 mutations.48 This study was performed from 2002 to 2014 and offered women either RRSO at age 35 or transvaginal ultrasonography plus CA 125 evaluation annually starting at age 24. The median age in those who opted for RRSO patients was 47 compared with 50 in the screening group. Of the 12 cancers identified, nine were found during screening, giving a total screening sensitivity of 70%. Ovarian cancer was too rare in the study to provide significant mortality data.48

A prospective cohort study in BRCA1 carriers by Gronwald et al in 2019 examined mortality in 1,196 women who enrolled in an ovarian cancer screening program with no RRSO and underwent at least one screening ultrasound evaluation vs 659 women who chose RRSO.49 The HR for preventive oophorectomy vs ultrasound screening was 0.23 (95% CI 0.05–0.97), indicating that ultrasound screening alone was not a viable alternative to preventive oophorectomy. Most other screening studies using pelvic ultrasonography or serum CA 125 evaluation or both have failed to show promising results, with no changes to mortality nor earlier stage of ovarian cancer detection.50–52 Thus, researchers have worked to develop other screening methods.

The use of ROCA has been hypothesized to improve on current ovarian cancer screening methods and has been used in several studies of high-risk women. Rosenthal et al published a prospective cohort study in 2017 that enrolled 4,348 women with 10% or higher risk for ovarian cancer in a single arm of the UK Familial Ovarian Cancer Screening Study and monitored them from 2007 to 2012 using ROCA screening every 4 months and transvaginal ultrasonography only.
annually if ROCA screen results were normal. These authors found that 38.5% (5/13) of screening-detected cancers were stage I or II (95% CI 13.9%–68.4%), indicating a possible shift to an earlier stage with the addition of ROCA. However, the positive predictive value was still only 10.8% (95% CI 6.5%–16.5%).

Another 2017 study by Skates et al also used ROCA, combining data from the prospective Cancer Genetics Network and Gynecologic Oncology Group trials, which included 3,692 women with a strong family history of breast or ovarian cancer or both or a known pathogenic variant in BRCA1 or BRCA2. These high-risk women were screened using serum CA 125 assessment every 3 months, which was evaluated using ROCA, and had transvaginal ultrasonography when significant increases in CA 125 were noted. Use of this algorithm in high-risk patients was able to identify six incidental ovarian cancers, with 50% in early stages (stage I–II), showing the same potential shift in stage as the UK Familial Ovarian Cancer Screening Study.

In the search for more efficacious screening, several other studies have combined the use of ROCA with transvaginal ultrasonography and other serum markers. A nested-control study of the UKCTOCS used serum markers protein Z, fibronectin, C-reactive protein, and CA 125 to create models to distinguish type I and type II ovarian cancer. In this study, published in 2017, Russell et al examined 418 serum samples from 49 different ovarian cancers and 31 controls for up to 6 years prior to the diagnosis of ovarian cancer and created models made to differentially detect ovarian cancer by type. The model for type II ovarian cancer detected high-grade serous cancer at an earlier stage than CA 125 alone or ROCA, with a potential 2–3 years of lead time.

A 2020 study combined CA 125 and ROCA with serum marker HE4 in a proof-of-concept prospective cohort study in California of BRCA1 and BRCA2 carrier women ages 30 and older who declined RRSO. The study assessed 149 women using the algorithm involving serum CA 125 and HE4 evaluation every 4 months and compared them with 43 women in a standard-of-care model using transvaginal ultrasonography and CA 125 assessment (with a threshold of >35 units/mL).
The average false-positive rate among women without ovarian cancer who had ROCA with CA 125 plus HE4 assessment and were referred for ultrasonography was 6.6% (specificity 93.4%). The false-positive rate for those who had ROCA with CA 125 plus HE4 assessment as well as ultrasonography and who were referred for surgical consultation was 1.7% (specificity 98.3%).

In terms of data specific to pathogenic mutations or hereditary genetic cancer predisposition syndromes other than BRCA1 or BRCA2, this review only found a single systematic review of ovarian cancer screening in Lynch syndrome. That systematic review identified 49 studies with a mean age of 45.3 years at the time of ovarian cancer diagnosis; 65% of tumors were diagnosed at an early stage (I or II). Six studies reported on ovarian cancer screening with transvaginal ultrasonography and CA 125. Of the 674 women in these studies, seven developed ovarian cancer during screening, and six of those cancers were found at an early stage. Although the studies were small, the authors were also not entirely surprised by the early stage of diagnosis given the propensity for the development of type I ovarian cancers among those with Lynch syndrome.

Other serum markers, circulating tumor cells, and algorithms have been suggested for screening for ovarian cancer, but we did not find any high-level evidence for their validity in high-risk women.

**Professional Guidelines and Recommendations for Ovarian Cancer Screening in High-Risk Women**

ACOG reports that there is no current strategy for ovarian cancer screening that has been proven to decrease mortality and that routine ovarian cancer screening is not recommended for women with BRCA mutations or family history of ovarian cancer. However, it does state that annual transvaginal ultrasonography and CA 125 assessment may be reasonable for patients starting at age 30–35 years until RRSO is performed, preferably within the recommended age range for the mutation. ACOG’s Practice Bulletin on Lynch syndrome states that there is no consensus on ovarian cancer screening for those with Lynch syndrome. It does comment on the distinctive biology of Lynch syndrome.


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ovarian cancers (type I vs type II ovarian cancers), which may mean that the results of ovarian cancer surveillance studies among those with BRCA1 or BRCA2 are not applicable to those with Lynch syndrome.

The American College of Radiology states that the use of transvaginal ultrasonography for ovarian cancer screening in premenopausal and postmenopausal women may be appropriate. The Society of Gynecologic Oncology and the American Society for Reproductive Medicine published a joint statement on hereditary gynecologic cancers that states that there is no effective ovarian cancer screening method but acknowledges that screening with transvaginal ultrasonography and CA 125 assessment may be an option for women who decline or defer RRSO. The European Society for Medical Oncology also states that there are no data proving that screening for ovarian cancer reduces mortality, but transvaginal ultrasonography and CA 125 assessment every 6 months can be considered for those at high risk beginning at age 30 with proper counseling on the lack of efficacy. NCCN states that, although high-level evidence is lacking, clinicians can consider, at their discretion, transvaginal ultrasonography and serum CA 125 assessment for patients starting at ages 30–35 years, especially in women who have elected not to undergo a RRSO.

The Royal College of Obstetricians and Gynaecologists recommends that ovarian cancer screening should not be offered as an alternative to RRSO. The Society of Obstetricians and Gynaecologists of Canada states that there are currently insufficient data to support ovarian cancer screening.

NCCN practice guidelines for genetic and familial risk assessment for breast, ovarian, and pancreatic cancer are the most frequently updated guidelines for providers looking for current guidance on screening recommendations for ovarian cancer and other cancer risks associated with various genetic mutations or hereditary cancer syndromes that carry an increased risk of hereditary ovarian cancer.

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DISCUSSION

In summary, ovarian cancer screening has not yet been definitively proven to decrease mortality from ovarian cancer, which is the end goal of such screening. A strength of our study is that we had several large-scale RCTs to support the finding that transvaginal ultrasonography in average-risk asymptomatic women is not beneficial. A weakness of the review is that large RCTs for ovarian cancer screening in high-risk women are not available because it would be unethical to withhold RRSO from the majority of high-risk women who have pathogenic variants. Additionally, broad applicability to all populations is limited, as most of the trials available had predominantly White participants. In the UKCTOCS and UK pilot studies, 95% of participants identified as White; in the PLCO study, 88% participants identified as White.\textsuperscript{15,20,21,25}

There are a lack of studies examining the efficacy of ovarian cancer screening in transgender and nonbinary patients, a group that would benefit from additional studies because they may use gender-affirming hormones and have reduced contact with health systems.\textsuperscript{58}

A major critique of the current studies is that they deem all ovarian cancer risk as the same. Some women with particular pathogenic mutations may be at risk for type I ovarian cancers, while others are at risk for type II ovarian cancers; these two categories of ovarian cancer have very different mortality and growth rates. Therefore, grouping them all as “ovarian cancer” and not accounting for the heterogeneity may contribute to some of the stage shifts and lack of mortality benefit in some of the studies of people at high risk. Studies used a variety of definitions of risk, and many did not differentiate mutation carriers from those who only had family histories of ovarian cancer. Using a standardized definition of those at high risk for ovarian cancer that includes genetic characterization would lead to a better assessment of the efficacy of different screening methods. Refinement of ovarian cancer screening with new biomarkers and algorithms, along with the new methods for identification of circulating tumor cells, might lead to more effective ovarian cancer screening approaches. In the meantime, ovarian cancer screening remains experimental, and age-appropriate RRSO remains the optimal approach for those at highest risk.
REFERENCES


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INTRODUCTION

This document summarizes the currently available evidence regarding the early diagnosis of ovarian cancer. The following questions were addressed through a literature search using the PICO format:

P = patient, problem, or population; I = intervention; C = comparison, control, or comparator; O = outcome(s)

1. **What are common presenting symptoms among people diagnosed with ovarian cancer? How predictive are these presenting symptoms of ovarian cancer?**

   **P:** Adults with ovarian cancer

   **I:** Presenting symptoms (abnormal uterine bleeding, abdominal or pelvic pain, distention, bloating, abdominal or pelvic mass, changes in bowel or bladder function, or constitutional symptoms [weight changes, early satiety, fevers, nausea, or vomiting]), symptom duration, and systematic symptom assessment

   **C:** Adults with one or more presenting symptoms vs no presenting symptoms

   **O:** Diagnosis of ovarian cancer, accurate prediction of ovarian cancer, incidence, stage at diagnosis, or survival rate

2. **In patients with symptoms, who should undergo evaluation for ovarian cancer? What are the most effective methods of evaluation for ovarian cancer?**

   **P:** Adults with persistent symptoms
I: Ovarian evaluation (pelvic examination, transvaginal ultrasonography, computed tomography [CT] scan, tumor markers, risk assessment algorithms or indexes, laparoscopy, magnetic resonance imaging [MRI], positron-emission tomography [PET] scan)

C: One evaluation method vs another vs observation

O: Diagnosis of ovarian cancer, test parameters (sensitivity, specificity, positive predictive value, negative predictive value, number needed to detect ovarian cancer, or risk of unnecessary intervention)

3. **In asymptomatic patients with an incidental finding of an ovarian cyst on transvaginal ultrasonography or CT, who should undergo evaluation for ovarian cancer? What are the most effective methods of evaluation for ovarian cancer?**

   **P:** Premenopausal vs postmenopausal asymptomatic patients with ovarian mass on transvaginal ultrasonography or CT imaging

   **I:** Ovarian evaluation (observation vs repeat imaging vs surgery)

   **C:** One evaluation method vs another vs observation; include image categorization like American College of Radiology (ACR) Ovarian-Adnexal Imaging-Reporting-Data System (O-RADS)

   **O:** Diagnosis of ovarian cancer or risk of unnecessary intervention

**METHODS**

A literature review was conducted by the American College of Obstetricians and Gynecologists’ (ACOG’s) Resource Center from the year 2000 to the present. Major professional society and health service guidelines, systematic reviews, meta-analyses, cohort studies, case–control studies, and randomized controlled trials (RCTs) published in English were included. Studies not available in English, case series, and case reports were excluded. The list was also limited to articles from countries classified as very high in the United Nations Human Development Index (http://hdr.undp.org/en/composite/HDI). Results were categorized according to the following levels of evidence:
• Level I: RCTs, systematic reviews, and meta-analyses
• Level II: Observational studies
• Level III: Guidelines and narrative reviews
• No level: References that were not fully indexed by level at the time of the literature search

Guidelines included in the search were related to screening, diagnosis, and risk factors for ovarian cancer and were retrieved from the websites of ACOG, the US Preventive Services Task Force, the Royal College of Obstetricians and Gynaecologists, the European Society for Medical Oncology, the American Society of Clinical Oncology, the National Comprehensive Cancer Network (NCCN), the Society of Obstetricians and Gynaecologists of Canada, the Society of Gynecologic Oncology, ACR, the National Institute for Health and Care Excellence (NICE), the European Society for Medical Oncology-European Society of Gynaecological Oncology consensus conference recommendations, ECRI Guidelines Trust, and the American Society for Reproductive Medicine.

For included research, title and abstract information for each study were reviewed by a single reviewer to determine relevance to the stated question. Full-text guidelines and articles were retrieved for the selected publications, and their findings were incorporated into this summary when appropriate.

RESULTS

The search identified major professional society guidelines, of which 44 were reviewed for relevance. Of these, 13 were directly applicable to the early diagnosis of ovarian cancer.

The initial article search resulted in 381 matches. The general search criteria were then broadened by combining the major Medical Subject Headings term *ovarian neoplasms* with general cancer terms in the title or abstract to capture

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additional results. This approach identified 1,061 studies. After reviewing title and abstract information, 93 papers were deemed relevant. Another 82 papers were excluded after review of the full text, leaving a total of 11 papers from the literature search included in this review. Seven additional papers and one guideline were identified by the primary reviewer as relevant to the research question as a result of review of references cited in the literature.

**What Are Common Presenting Symptoms among People Diagnosed with Ovarian Cancer? How Predictive Are These Presenting Symptoms of Ovarian Cancer?**

A systematic review of international guidelines published before March 13, 2018, was conducted by Funston et al.¹

Figure 1 shows the frequency with which symptoms associated with ovarian cancer are mentioned in various guidelines.

![Figure 1. Frequency of Ovarian Cancer Symptom Mentioned in International Guidelines*](image)


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The associated diagnostic accuracies of some of these symptoms were reported in a systematic review of studies.² The review identified cohort or case–control studies that had data on symptoms, combinations of symptoms, or medical history information present prior to the diagnosis of ovarian cancer. The presence of abdominal mass (positive likelihood ratio [+LR], 30.0), abdominal distention or increased girth (+LR 16.0), abdominal or pelvic pain (+LR 10.4), abdominal or pelvic bloating (+LR 9.3), and loss of appetite (+LR 9.2) had the highest likelihood ratios of being associated with an ovarian cancer diagnosis. The specificities associated with these symptoms range from 88% to 99%; however, the sensitivities are all less than 50%.
The same review also analyzed the performance of four published symptom indices on the aggregate data and compared receiver operating characteristic curves with individual symptoms for the diagnosis of ovarian cancer: the Goff Ovarian Cancer Symptom Index, the Grewal symptom score, and two index scores proposed by Lim and colleagues (see Figure 2).² The combined sensitivity of the Goff Index (after elimination of one study that appeared to be a statistical outlier) was 63%, resulting in an overall specificity of 95% and a +LR of 12.6. The Grewal symptom score had sensitivity, specificity, and +LR of 73%, 91%, and 8.37, respectively. The values for Lim et al’s index 1 (83%, 81%, and 9.2)
and index 2 (78%, 94%, and 13.1) were similar. The authors noted that the work by Grewal and Lim should be considered cautiously, as neither has supporting independent validation studies.

A case–control study conducted in England included 212 women with ovarian cancer and 1,060 age- and general-practice-matched controls. The authors reviewed blinded charts of all the participants for reported symptoms prior to diagnosis. The study calculated odds ratios (ORs) and positive predictive values from a conditional logistic regression analysis. The OR for abdominal distention was the highest at 240, with a confidence interval (CI) of 46 to 1,200. Postmenopausal bleeding (OR 24, 95% CI 9.3–64), loss of appetite (OR 17, 95% CI 6.1–50), urinary frequency (OR 16, 95% CI 5.6–48), abdominal pain (OR 12, 95% CI 6.1–22), rectal bleeding (OR 7.6, 95% CI 2.5–23), and abdominal bloating (OR 5.3, 95% CI 1.8–16) were statistically increased. A second multivariate analysis was performed excluding symptoms that were reported in the final 180 days before diagnosis. Abdominal distention (OR 18, 95% CI 2.1–160), urinary frequency (OR 3.1, 95% CI 1.3–7.3), and abdominal pain (OR 2.6, 95% CI 1.5–4.6) remained significant. When used alone as an indicator of ovarian cancer, only abdominal distention had a positive predictive value of greater than 1% (OR 2.5, 95% CI 1.2–5.0). Pairing symptoms only showed a modest increase in positive predictive value, which remained in the single digits.

A 2007 study by Goff et al surveyed women who were undergoing surgery for a pelvic mass, women undergoing ultrasonography for pelvic organ assessment, and a group of healthy high-risk women who were enrolled in the Ovarian Cancer Early Detection Study.4 Participants completed a survey that asked about 23 symptoms that have all previously been associated with ovarian cancer. An initial set of patients from the three groups was used to develop an ovarian cancer symptom index using bivariate analysis followed by logistic regression modeling. The results were then applied to a second set of patients. The results found the best correlation with symptoms that were less than 12 months in duration and present for more than 12 days out of the month. Pelvic or abdominal pain, increased abdominal size or bloating, urinary frequency or urgency, and feeling full or having difficulty eating had the greatest association with the
diagnosis of ovarian cancer. The authors suggest that a patient reporting any one of these six symptoms (pelvic or abdominal pain, increased abdominal size or bloating, difficulty eating, or feeling full) for the specified duration should be considered screen-positive. The index had a sensitivity of 56.7% for early-stage disease and 79.5% for advanced-stage disease. The specificity was 90% for women 50 and older and 86.7% for women younger than 50.

Additional research has looked at the time to diagnosis of type I versus type II epithelial ovarian cancers using questionnaires and primary care records collected before diagnosis. Symptoms had to have been new in the past 15 months to be considered related to the diagnosis. Symptoms were further divided into four groups: abdominal, gastrointestinal, gynecologic, and systemic. The authors found that the time to diagnosis and first symptom reported were similar in patients with type I and type II invasive epithelial ovarian cancer.

Other efforts have focused on relating disease stage to the type of symptoms that patients experience. Data collected from the National Cancer Institute’s Surveillance, Epidemiology, and End Results database from 1995 to 1999 were used to perform a retrospective cohort study on ovarian cancer patients. Patients with at least 12 months of Medicare enrollment before the diagnosis of ovarian cancer had their charts reviewed for diagnosis codes that would indicate either gynecologic (abdominal or pelvic swelling, abnormal bleeding, or genital pain), gastrointestinal (abdominal pain, constipation, diarrhea, weight gain or loss, nausea, vomiting, distention, early satiety, or intestinal obstruction), or other (not gynecologic or gastrointestinal) symptoms. Patients were grouped by spread of disease, where local was considered to correlate with the International Federation of Gynecology and Obstetrics (FIGO) stage IA and IB, regional disease was FIGO stage IC or II, and distant disease was FIGO stage III or IV. Overall, 81.6% of patients had at least one symptom or diagnosis potentially related to their ovarian cancer. The authors found that gynecologic symptoms were more likely to occur in patients with earlier stage disease compared with women with gastrointestinal symptoms.
Survival data have been described in relation to the presence of ovarian cancer symptoms in patients with a confirmed invasive epithelial ovarian cancer. An analysis was performed on patients enrolled in the United Kingdom Collaborative Trial of Ovarian Cancer Screening who did not undergo screening. Presence and duration of symptoms were determined by review of medical and study records. Patients with symptoms for fewer than 12 months before diagnosis were considered symptomatic. Patients were grouped using the NICE criteria (abdominal or pelvic pain, increased abdominal size or bloating, loss of appetite or feeling full, and increased urinary urgency or frequency) or modified Goff Symptom Index (abdominal or pelvic pain, increased abdominal size or bloating, and loss of appetite or feeling full). A total of 574 patients were diagnosed with invasive epithelial primary tubo-ovarian cancer. Of these patients, 90.8% reported symptoms, with about two thirds meeting either the NICE or Goff symptom criteria. Significantly worse survival was seen in women presenting with either NICE or modified Goff symptoms compared with those with no symptoms. A woman’s risk of death increased by 20% for each additional symptom beyond the first.

ACOG guidelines indicate that there is a role, albeit limited, for the use of symptoms to guide additional investigation into potential presence of ovarian cancer. In particular, increasing abdominal size, bloating, abdominal or pelvic pain, difficulty eating, or early satiety are associated with increased odds of having ovarian cancer. New onset of these symptoms (<12 months) with persistence for more than 12 days out of the month are potentially relevant. Of special note, these symptoms are also relatively common among women with other disease processes.

NICE echoes these symptom triggers, with an emphasis on women 50 and older and adds increased urinary urgency or frequency, unexplained weight loss, fatigue, or changes in bowel habits as potential indicators for additional testing.
In Patients with Symptoms, Who Should Undergo Evaluation for Ovarian Cancer? What Are the Most Effective Methods of Evaluation for Ovarian Cancer?

No studies were found using imaging, biomarkers, risk algorithms, or multimodal risk assessment tools for primary evaluation of patients with symptoms associated with ovarian cancer.

Professional society guidelines about when to initiate an evaluation based on symptoms vary. ACOG recommends that women with more than 12 days per month of new-onset symptoms (duration <12 months) should have their symptoms evaluated, with ovarian cancer included in the differential diagnosis. NCCN guidelines further specify that if symptoms are becoming more severe, evaluation is warranted. NICE guidelines add that particular attention should be given to women over age 50 with symptoms.

ACR maintains an updated list of appropriateness criteria based on clinical conditions. For symptoms that may indicate an evaluation for ovarian cancer, only subacute pain in postmenopausal patients is listed, although ACR also gives criteria based on asymptomatic, clinically suspected adnexal masses. Both criteria are further divided based on clinical scenarios, such as menopausal status, suspicion of benign or malignant mass, location of pain (vulvar, perineal, vaginal, or pelvic), and other variables. Ultrasonography of the pelvis, transabdominal and transvaginal, with duplex Doppler, is listed as “usually appropriate” (the highest level) for each of these scenarios as the initial imaging modality. MRI (positive or negative contrast) is generally listed as “may be appropriate” (second highest level), and CT of the pelvis (with or without abdominal views) with contrast is “usually not appropriate.” One exception is the use of CT of the pelvis with contrast to assess chronic pain in postmenopausal patients, which is listed as “may be appropriate.”

ACOG’s Evaluation and Management of Adnexal Masses (Practice Bulletin no. 174) lists transvaginal ultrasonography with Doppler as the most-used and the recommended imaging technique for the evaluation of adnexal masses. CT, MRI, and PET are not recommended for the initial evaluation of adnexal masses.
The European Society for Medical Oncology recommends patients with symptoms have a full clinical evaluation.\textsuperscript{15}

Although it is recognized that cancer antigen (CA) 125 is frequently measured, it has limited utility in ovarian cancer, as only about 50\% of patients will have elevated CA 125 at stage I.\textsuperscript{15} The elevation rate is higher in advanced disease, but up to 15\% of these patients will also have a normal CA 125 level. For cancer identification, CA 125 lacks specificity as well, with elevations also present in noncancerous conditions, such as endometriosis, pelvic inflammatory disease, and some benign ovarian tumors. When there is adequate suspicion of gastrointestinal origin, assessing serum carcinoembryonic antigen and CA 19-9 levels, as well as gastroscopy and colonoscopy, can be helpful in determining tumor origin. The European Society for Medical Oncology identifies ultrasonography as the first-line imaging modality for assessment of the ovaries because it can provide a visual depiction of ovarian structures and be used to identify structural details that can help diagnose an ovarian cancer. CT is recommended as a secondary modality to assess the extent of disease and for surgical planning when a cancer is suspected.

In contrast, NICE guidelines recommend CA 125 assessment as the first step in evaluating women with symptoms for detection in primary care.\textsuperscript{11} For those with CA 125 levels higher than 35 IU/mL, transvaginal ultrasonography is recommended to evaluate for the presence of a cancer.

In Asymptomatic Patients with an Incidental Finding of an Ovarian Cyst on Transvaginal Ultrasonography or CT, Who Should Undergo Evaluation for Ovarian Cancer? What Are the Most Effective Methods of Evaluation for Ovarian Cancer?

The initial evaluation of a patient with an adnexal mass should be considered in the context of individual risk factors. The risk of ovarian malignancy rises with age, with 69.4\% of ovarian malignancies being diagnosed in women over age 55.\textsuperscript{14} Patients with a familial cancer syndrome, such as \textit{BRCA1}, \textit{BRCA2}, or Lynch syndrome, are at particularly high risk. ACOG recommends eliciting a family history and performing a physical examination for clues about the potential malignancy of
an adnexal mass, although there is considerable overlap with other benign gynecologic conditions.\textsuperscript{14} Transvaginal ultrasonography with spectral color Doppler is the recommended imaging modality; however, ACOG notes that some limited evidence supports the use of MRI when the origin of a mass cannot be determined by transvaginal ultrasonography. This finding is in line with ACR appropriateness criteria for the evaluation of asymptomatic adnexal masses in women, regardless of menopausal status.\textsuperscript{12}

ACOG discusses ultrasound characteristics of ovarian masses that are suggestive of benign disease and, therefore, may be appropriate for observation.\textsuperscript{14} Simple appearance (absence of septations, solid components, or internal blood flow), suspected endometriomas (homogeneous round cysts containing low-level echoes), mature teratomas (hypoechoic attenuating components with multiple small homogeneous interfaces), and hydrosalpinges (tubular-shaped sonolucent cysts) have a high diagnostic specificity on ultrasonography and are usually benign. Of particular note, simple cysts, even in postmenopausal women, carry a very low risk of cancer and frequently spontaneously regress. There are also ultrasound features that should raise concerns about the possibility of malignancy. These include cyst size greater than 10 cm, papillary or solid components, irregularity, presence of ascites, and high color Doppler flow. Multiple ultrasound scoring systems have been developed as a method to detect cancers of the ovary. The most accurate appear to be the International Ovarian Tumor Analysis (IOTA) group’s Logistic Regression 2 model and IOTA Simple Rules. The sensitivity and specificity of the Logistic Regression 2 model (with a cutoff of 10%) are 92% (88%–95%) and 83% (77%–88%), respectively, for the diagnosis of ovarian cancer (with borderline tumors being counted in the same category as malignancy). Similarly, Simple Rules has a sensitivity of 93% (89%–95%) and specificity of 81% (76%–85%). Most of the research on these scoring systems has been conducted with specially trained sonographers; therefore, it is unknown how these systems would perform in different clinical settings.

Serum marker testing is indicated as part of ovarian cancer risk assessment in patients with an adnexal mass. CA 125 has a sensitivity in the range of 61% to 90% and a specificity of 71% to 93%.\textsuperscript{14} The broad ranges of these reported figures

\textbf{Burke W, Barkley J, Barrows E, Brooks R, Gesci K, Huber-Keener K, et al. Executive Summary of the Ovarian Cancer Evidence Review Conference. Obstet Gynecol 2023;142.} The authors provided this information as a supplement to their article. ©2023 The Authors.
reflect considerable overlap in both benign (in which CA 125 can be elevated) and malignant (in which CA 125 can be normal) conditions. Most CA 125 elevations in benign conditions occur before menopause. Incidence data indicate that most ovarian cancers occur after menopause; therefore, postmenopausal women with an elevated CA 125 are at particularly high risk of having an ovarian malignancy. ACOG suggests measuring ß-hCG, L-lactate dehydrogenase (LDH), alpha-fetoprotein (AFP), or inhibin when less common ovarian histopathology is suspected.

ACOG does not recommend the use of biomarker panels, such as the multivariate index assay and Risk of Ovarian Malignancy Algorithm, in the initial workup of adnexal masses. ACOG states that these panels may be used in place of CA 125 when considering which patients should be managed with referral to or in consultation with a gynecologic oncologist. The addition of clinical assessment or imaging increases the sensitivity of the multivariate index assay. As a single test, the multivariate index assay has a sensitivity of 91.4% in early-stage disease. This increases to 95.3% when clinical assessment is included and 98% and 97% with the use of ultrasonography and CT, respectively.

ACOG suggests that asymptomatic adnexal masses that appear benign on ultrasonography, particularly in the presence of a normal CA 125 level, may be expectantly managed. In addition to the above-described benign findings, lesions with characteristic features of endometriomas, mature teratomas, or hydrosalpinges seen on ultrasonography can be managed expectantly. When the diagnosis is uncertain and cancer remains a potential concern, repeat imaging is recommended; however, the appropriate follow-up interval has not been defined. ACOG suggests limiting the observation of masses that do not have any changes on ultrasonography to 1 year for lesions without solid components and 2 years for masses that do contain solid components, although this suggestion is based on expert opinion.

The Royal College of Obstetricians and Gynaecologists’ Green-top Guideline on the management of suspected ovarian masses in premenopausal patients recommends against measuring CA 125 in sonographically identified simple ovarian cysts. The use of additional serum markers (LDH, human chorionic gonadotropin, and AFP) is recommended for all
women under age 40 with a complex adnexal mass. Transvaginal ultrasonography is the preferred imaging modality, with MRI and CT being reserved for more complex cases when malignant disease is a possibility. Malignancy risk estimation is considered an essential tool for ovarian mass assessment. The Royal College of Obstetricians and Gynaecologists specifically discusses use of the Risk of Malignancy Index I with a cutoff of 200. It also lists the IOTA Simple Rules as a method to perform risk assessment without a CA 125 level. The Royal College of Obstetricians and Gynaecologists does not recommend follow-up for simple ovarian cysts that are less than 5 cm, as these usually resolve spontaneously. Simple cysts in the 5–7-cm range should be monitored with annual ultrasonography. When a simple cyst is larger than 7 cm, MRI can be considered as an adjunct if surgical removal is not planned. When under surveillance, cysts that persist or grow should be considered for removal.

A joint guideline from the Society of Gynecologic Oncology of Canada and the Society of Obstetricians and Gynaecologists of Canada recommends that adnexal masses be evaluated using either pattern recognition (by an expert ultrasonographer) or a risk prediction model developed by IOTA. Referral to a gynecologic oncologist is recommended when high-risk features are seen on ultrasonography, including a solid component with strong or central color flow; more than three papillary projections; multiple, thick, irregular septations; ascites; or peritoneal nodularity. Women with adnexal masses that have indeterminate features should be evaluated by an expert sonographer or by MRI. The Society of Gynecologic Oncology of Canada and Society of Obstetricians and Gynaecologists of Canada also recommend the use of additional serum markers in women under 40, such as LDH, ß-hCG, and AFP. When a cancer is suspected, additional tumor markers (carcinoembryonic antigen, CA 19-9, and CA 15-3) and CT of the chest, abdomen, and pelvis may be considered to look for alternative primary tumor locations and to assess the extent of disease.

The Society of Obstetricians and Gynaecologists of Canada also gives specific guidance on the management of asymptomatic adnexal masses that appear to be benign, which includes most asymptomatic masses less than 10 cm in diameter that are characterized as benign on ultrasonography. It recommends repeating ultrasonography in 8–12
weeks, during the proliferative phase if feasible. For masses that remain stable, annual follow-up can be continued. When surgery is indicated because of symptoms, cystectomy should be considered for premenopausal patients, and unilateral versus bilateral oophorectomy can be considered for postmenopausal patients. For perimenopausal patients, shared decision making should be employed to discuss the method of mass removal (cystectomy versus oophorectomy). Surgical evaluation should include assessment of the pelvic and abdominal viscera for evidence of disease. Biopsies and washings are indicated for abnormal findings.

At the secondary care level (ie, in patients with an identified adnexal mass), CA 125 testing is also recommended by NICE, with addition of AFP and ß-hCG assessment for women under 40. Ultrasonography of the abdomen and pelvis is the first-line imaging test, with CT reserved for assessment of the extent of disease in those patients in whom prior testing suggests ovarian cancer. NICE guidelines recommend calculating a risk score using the Risk of Malignancy Index I based on the ultrasonography and CA 125 results (see Box 1). Patients with a score of 250 or higher on the Risk of Malignancy Index I should be referred to a specialist multidisciplinary team. The routine use of MRI is not recommended for pelvic imaging.
Box 1. Risk of Malignancy Index I*

Risk of Malignancy Index I = U × M × serum CA 125

U = 0 for ultrasound score of 0
    1 for ultrasound score of 1
    3 for ultrasound score of 2–5

M = 1 if premenopausal
    3 if postmenopausal

Ultrasound score: Assign one point for each of the following:

- Multilocular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Presence of bilateral lesions


https://www.nice.org.uk/guidance/dg31

NICE compared more recently developed ovarian cancer assessment tools with the Risk of Malignancy Index I model with a cutoff of 250 (see Table 1).20 These included the Risk of Malignancy Index I with a lower cutoff (200), the IOTA Assessment of Different Neoplasias in the Adnexa (ADNEX) model, the second-generation multivariate index assay serum test, the Risk of Ovarian Malignancy Algorithm, several human epididymis protein 4 assays, and IOTA Simple...
Rules. Evidence was reviewed with the goal of identifying tools that could be practically implemented by secondary care providers to correctly identify cancers versus benign ovarian masses and to evaluate cost effectiveness. NICE concluded that the lack of availability of ultrasound expertise made the two IOTA models impractical for nationwide implementation. The remaining tests had insufficient evidence (particularly direct comparisons with the Risk of Malignancy Index I) or were drawn from populations with too high a prevalence of cancer to make definitive conclusions about their accuracy. The 200 threshold for the Risk of Malignancy Index I did not sufficiently alter the accuracy of the test to recommend changing the cutoff. There was too much uncertainty about the costs of posttest care to complete a cost-analysis model.

Table 1: Comparison of Ultrasound, Biomarker, and Multimodal Risk Assessment Tools*

<table>
<thead>
<tr>
<th>Test</th>
<th>Features</th>
<th>Year of FDA Approval</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIA2G21</td>
<td>5 analytes: CA 125, apolipoprotein A-1, transferrin, FSH, and HE4</td>
<td>2016</td>
<td>91.3% (83.8–95.5)</td>
<td>69.1% (64.4–73.4)</td>
</tr>
<tr>
<td>ROMA22</td>
<td>2 analytes: HE4, CA 125</td>
<td>2011</td>
<td>Postmenopausal: 90.2% (78.6–96.7)</td>
<td>Postmenopausal: 76.0% (68.4–82.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Premenopausal: 81.3% (54.4–96.0)</td>
<td>Premenopausal: 4.2% (68.1–79.7)</td>
</tr>
<tr>
<td>Multivariate Index Assay23</td>
<td>5 analytes: CA 125, prealbumin,</td>
<td>2009</td>
<td>92.2% (88.2–94.9)</td>
<td>49.4% (45.9–53.0)</td>
</tr>
</tbody>
</table>

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| Risk of Malignancy Index I (cutoff >250$^{24}$) | CA 125, menopausal status, ultrasound scan score | — | 78% (62.4–89.4) | 99.0% (94.5–100) |
| IOTA Simple Rules$^{25}$ | Ultrasound assessment (conclusive, 77% of masses) | — | 92% (89–94)$^\dagger$ | 96% (94–97)$^\dagger$ |
| IOTA ADNEX$^{26}$ | Ultrasound assessment, CA 125, and patient characteristics | — | 96.5% (95.2–97.6)$^\ddagger$ | 71.3% (68.9–73.3) $^\ddagger$ |


$^\dagger$For masses with a conclusive result

$^\ddagger$Cut-off of 10%

Abbreviations: ADNEX, Assessment of Different Neoplasias in the Adnexa; FDA, US Food and Drug Administration; FSH, follicle stimulating hormone; HE4, human epididymis protein 4; IOTA, International Ovarian Tumor Analysis group; MIA2G, second-generation multivariate index assay; ROMA, Risk of Ovarian Malignancy Algorithm
ACR published guidelines in 2020 on risk stratification and management for adnexal masses, known as O-RADS. The guidelines give a comprehensive systematic means to describe and classify masses of the adnexa into risk categories (see Table 2). Much of the terminology and ultrasound techniques are directly adapted from those used by the IOTA group.

Table 2. American College of Radiology Ovarian-Adnexal Imaging-Reporting-Data System (O-RADS) Categories*

<table>
<thead>
<tr>
<th>O-RADS Score</th>
<th>Risk Category [IOTA Model]</th>
<th>Lexicon Descriptors</th>
<th>Management Pre-menopausal</th>
<th>Management Post-menopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Incomplete Evaluation [N/A]</td>
<td>N/A</td>
<td>Repeat study or alternate study</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Normal Ovary [N/A]</td>
<td>Follicle defined as a simple cyst ≤ 3 cm</td>
<td>None</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Corpus Luteum ≤ 3 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Almost Certainly Benign (&lt; 1%)</td>
<td>Simple cyst ≤ 3 cm</td>
<td>N/A</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;3 cm to 5 cm</td>
<td>None</td>
<td>Follow up in 1 year *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 cm but ≤ 10 cm</td>
<td>Follow up in 6 - 12 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Classic Benign Lesions</td>
<td>See Figure 3 for separate descriptors</td>
<td>See Figure 3 for management strategies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-simple unilocular cyst, smooth inner margin ≤ 3 cm</td>
<td>None</td>
<td>Follow up in 1 year * if concerning, US specialist or MRI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 3 cm but ≤ 10 cm</td>
<td>Follow up in 6 - 12 weeks if concerning, US specialist or MRI</td>
<td>US specialist or MRI</td>
</tr>
<tr>
<td>3</td>
<td>Low Risk Malignancy (1-10%)</td>
<td>Unilocular cyst ≤ 10 cm (simple or non-simple)</td>
<td>US specialist or MRI Management by gynecologist</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Typical dermoid cysts, endometriomas, hemorrhagic cysts ≤ 10 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unilocular cyst, any size with irregular inner wall &lt;3 mm height</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multilocular cyst &lt; 10 cm, smooth inner wall, CS = 1-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solid smooth, any size, CS = 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Intermediate Risk (10-&lt;50%)</td>
<td>Multilocular cyst, no solid component ≥ 10 cm, smooth inner wall, CS = 1-3</td>
<td>US specialist or MRI Management by gynecologist with GYN-oncologist consultation or solely by GYN-oncologist</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any size, smooth inner wall, CS = 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any size, irregular inner wall and/or irregular septation, any color score</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unilocular cyst with solid component Any size, 0-3 papillary projections, CS = any</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multilocular cyst with solid component Any size, CS = 1-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solid Smooth, any size, CS = 2-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>High Risk (≥50%)</td>
<td>Unilocular cyst, any size, ≥ 4 papillary projections, CS = any</td>
<td>GYN-oncologist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multilocular cyst with solid component, any size, CS = 3-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solid smooth, any size, CS = 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solid irregular, any size, CS = any</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ascites and/or peritoneal nodules**</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*At a minimum, at least 1-year follow-up showing stability or decrease in size is recommended with consideration of annual follow-up of up to 5 years, if stable. However, there is currently a paucity of evidence for defining the optimal duration or interval of timing for surveillance.


**Presence of ascites with category 1-2 lesion, must consider other malignant or nonmalignant etiologies of ascites.

Abbreviations: CS, color score; GYN, gynecologic; IOTA, International Ovarian Tumor Analysis group; N/A, not applicable; MRI, magnetic resonance imaging

A 2021 study compared the results of 150 patients with an ultrasound-diagnosed adnexal mass using the IOTA Simple Rules, IOTA Simple Rules risk assessment, ADNEX model, and O-RADS.28 The final diagnosis was confirmed by histopathology, and the time interval from ultrasound detection to surgical removal did not exceed 180 days. The ADNEX model was applied prospectively without the inclusion of CA 125 level. The other models were applied retrospectively through review of the ultrasound findings. The area under the receiver operating characteristics curve was calculated for the Simple Rules risk assessment and ADNEX models. The distribution of malignancies was also reported using the O-RADS classification. The area under the receiver operating characteristics curve was 0.937 for ADNEX and 0.941 for Simple Rules risk assessment. Of the 40 histologically confirmed cases of cancer, 100% corresponded to an O-RADS category 4 or 5. The calculated rate of malignancy in O-RADS category 4 was 21.2%, and for
O-RADS category 5, it was 78.8%. The authors concluded that all four models performed well on their patient group and that the IOTA models had better specificity than O-RADS.

Patients with an identified ovarian mass who took part in an ovarian cancer screening program at the University of Kentucky were monitored with serial ultrasonography in intervals between 6 weeks and 6 months. Abnormalities were defined as an ovarian volume more than two standard deviations above normal, the presence of cysts with septations, solid areas, papillary projections, and solid echogenic structures. Surgery was performed if there was progression in the morphology (growth of solid components) or size of the tumor or if patients became symptomatic. The addition of surveillance for abnormal ultrasound findings resulted in a rise of the positive predictive value of an abnormal scan from 8.1% to 24.7%. Serial ultrasound use was also associated with a shift in stage of detection, with most cancers being diagnosed at an early stage (I or II).

Risk of complications during follow-up of expectant management of suspected benign ovarian lesions has also been studied. A 2-year interim analysis of patients enrolled in the IOTA-5 study was reported by Froyman et al. IOTA-5 is an ongoing prospective, multicenter, cohort study that includes patients with an adnexal mass who are selected for surgery versus conservative management. For the interim analysis, patients were grouped by outcomes, including spontaneous resolution, surgical removal of mass, or death from any cause. The group that had surgical removal was further classified by the reason for surgery and findings at surgery. Of 1,919 patients with a mass that was newly detected during the study period and assessed as benign who had outcomes examined at 24 months following enrollment, 20.2% had spontaneous resolution of their mass during follow-up, and 16.1% had surgical intervention. The most common reason for surgical intervention was patient request (9.5%). For 82.5% of patients, the mass either resolved or they remained in follow-up at the 2-year mark. The risk of complications of surgery was less than 0.5% when the final diagnosis was invasive malignancy, borderline tumor, torsion, or cyst rupture.
In a retrospective observational study of ovarian teratomas diagnosed by ultrasonography, patients who were asymptomatic with a tumor that did not appear to be growing rapidly (>10 mm in 6 months) or that did not develop characteristics that suggested malignancy were offered serial surveillance. Ultrasound examinations were initially performed at 3 and 6 months and then yearly thereafter. If changes occurred on follow-up or if the patient developed symptoms, the mass was surgically removed. The mean growth rate of suspected teratomas that were eventually removed was 4.8 mm/year. Those that were not removed (n = 278) had a mean growth rate of 0.6 mm/year. There was one confirmed case of torsion in the expectantly managed group of patients (0.2%).

**DISCUSSION**

The early diagnosis of ovarian cancer has been an elusive clinical question because of the rapid, and initially silent, progression of the disease. In the early stages, tumor markers are frequently negative, and patients are asymptomatic. Additionally, many benign conditions can cause tumor marker elevations, cancer-like symptoms, and findings on diagnostic imaging that make separating benign disease from early-stage cancer difficult. One potential clue regarding symptom development is the subacute duration and overall frequency of symptoms. Efforts to educate patients and clinicians about these clues have not resulted in earlier diagnosis.

Transvaginal ultrasonography is superior to other imaging modalities in the initial assessment of symptoms that trigger a workup for ovarian cancer. When the ovaries are visualized as normal, the negative predictive value of the ultrasound examination is extremely high. While some professional guidelines have advocated assessment of CA 125 as an alternative initial test, it is only a viable option when transvaginal ultrasonography is not available because of its poor negative predictive value in ovarian cancer. When a postmenopausal patient has an elevated CA 125 level and abnormal ultrasound results, further evaluation should be performed to rule out cancer, because of the high risk of malignancy in this group.


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There have been significant advancements in the characterization of benign ovarian ultrasound findings. Simple cysts can be thought of as almost universally benign, even in postmenopausal patients, up to a threshold of at least 10 cm. Simple cysts larger than 10 cm are also frequently benign; however, subtle mass characteristics that would characterize them as more complex become easier to miss as the cyst size increases. The diagnosis of some benign conditions, such as teratomas, endometriomas, and hydrosalpinges, are reliable enough that surveillance is a reasonable option for many patients. The addition of follow-up imaging workflows for indeterminate ultrasound findings may hold the key to future advancements in the early detection of ovarian cancer and the reduction of surgical burden.

The investigation into the various biomarker assays has given clinicians a variety of tests that have been advocated as a means for the general gynecologist to triage patients at low risk when determining whether surgery is needed. Multimodal and other ultrasound assessment algorithms appear to accurately distinguish benign from malignant disease when performed by a competent examiner.

**RESEARCH GAPS**

As previously noted, symptom screening is fraught with overlap with benign conditions and may never be sensitive enough to detect early-stage disease. The data on the use of various assays and assessment tools will require larger comparative studies to investigate their best use. Additional studies of ultrasound characterization and morphology algorithms are needed to prove their utility when employed by sonographers in different centers with different backgrounds, training, and expertise. Investigations into the combination of ultrasonography and biomarker assays to maximize the potential for diagnosis have not been conducted to a significant degree. Many of the studies that have investigated the various modalities of early ovarian cancer detection have also had a high incidence of cancer that is not representative of the general population. Therefore, it is unknown how well these modalities will perform in large, population-based studies. Additional investigations into the detection of circulating tumor cells also have the potential to improve detection, but high-quality studies are lacking.


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Burke W, Barkley J, Barrows E, Brooks R, Gesci K, Huber-Keener K, et al. Executive Summary of the Ovarian Cancer Evidence Review Conference. Obstet Gynecol 2023;142. The authors provided this information as a supplement to their article.
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Ovarian Cancer Literature Review

Appendix 7. Overview of Diagnosis and Care Coordination for the Primary Care Provider

Primary Reviewer: Rebecca Brooks, MD

Secondary Reviewer: Shirley Mei, MD

INTRODUCTION

This document addresses what the primary care provider should know about the diagnosis and care coordination for a patient with ovarian cancer. The literature search aimed to identify current major professional society and health service guidelines for the following:

- Standard care evaluation of symptoms and incidentally found masses
- Criteria for referral to a gynecologic oncologist

This literature review also seeks to describe the usual trajectory after referral to a gynecologic oncologist, with emphasis on guidelines when possible, to set expectations and provide anticipatory guidance for patients.
METHODS

The American College of Obstetricians and Gynecologists’ (ACOG’s) Resource Center searched Cochrane, Medline through Ovid, and PubMed databases using a search strategy based on the goals described. Results were categorized according to the following levels of evidence:

- Level I: Randomized controlled trials (RCTs), systematic reviews, and meta-analyses
- Level II: Observational studies
- Level III: Guidelines and narrative reviews
- No level: References that were not fully indexed by level at the time of the literature search

Relevant guidelines from ACOG, the American College of Radiology, the American Society of Clinical Oncology, the American Society for Reproductive Medicine, the European Society for Medical Oncology, the National Comprehensive Cancer Network (NCCN), the National Institute for Health and Care Excellence (NICE), the Society of Gynecologic Oncology, and the US Preventive Services Task Force were identified and prioritized for review. A single investigator reviewed the title and abstracts of all articles and guidelines, followed by full manuscript review of those meeting criteria for inclusion. The reference list and bibliography of included articles were reviewed to identify other relevant works not identified by the primary search.

Inclusion criteria were major professional society or health service guidelines, systematic reviews, meta-analyses, cohort studies, case–control studies, and RCTs published in 2000 or later. Only articles available in English were included. Case reports, case series, and articles unavailable in English were excluded.


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To streamline data retrieval, systematic reviews and meta-analyses were prioritized. The individual studies included in such reviews were not separately included in this review unless they provided additional pertinent information. Nonsystematic review articles were generally excluded unless there was a lack of high-quality studies on a specific topic.

RESULTS

Literature Summary

The literature review prioritized high-level reviews and ACOG, NCCN, Society of Gynecologic Oncology, American Society of Clinical Oncology, and European Society for Medical Oncology consensus statements and committee opinions. Of the guidelines identified, nine were included, serving as the foundation for this review. Four guidelines were reviewed and excluded because they were older or not US-based (and therefore less relevant to the population given different genetic and health care system factors).

The literature search found six level I RCTs, but all were excluded after title review as not relevant to the topic. It also found 11 level I systematic reviews and meta-analyses. Of these, seven were excluded because they were not relevant.

The search identified 145 studies that were categorized as level II evidence. Of these, 114 were excluded after review of the title for the following reasons: not relevant to topic, covered in other sections, wrong disease site, not relevant to the US population, consisted of case reports or case series, or the topic was better covered or more clinically relevant in other sources with a stronger level of evidence (eg, professional guidelines and practice bulletins from NCCN, ACOG, the Society of Gynecologic Oncology, or the American Society of Clinical Oncology). Of the remaining, 31 were reviewed.
further; nine were included, and 22 were excluded for various reasons (primarily because they were not relevant or went beyond the scope of this topic).

The search found 93 level III studies. Of these, 78 were excluded based on review of the title alone because they addressed the wrong disease site, were not relevant, or were guidelines from other countries (in cases in which strong US guidelines existed). Of the remaining, 15 were reviewed for content; one was included, and 14 were excluded for various reasons, mostly because they were beyond the scope of this review.

No level of evidence was assigned to 74 studies. Of these, 63 were excluded after review of the title review because they were not relevant, were already covered in a larger analysis, or addressed the wrong disease site. Of the 11 reviewed in greater depth, one was included; 10 were excluded, generally because they were not relevant.

Further review of the PubMed database yielded 93 more studies. Of these, 87 were excluded after review of the title because they were either case reports or case series, were not applicable to the US population, or were not relevant to this section. Six were reviewed in greater depth; four were included, and two were excluded because they were less relevant or were addressed by sources of higher-quality evidence.

**Standard Care Evaluation of Symptoms and Incidentally Found Masses**

ACOG’s “Evaluation and Management of Adnexal Masses” (Practice Bulletin no. 174) is an excellent reference for providers.¹ The differential diagnosis of apparent masses of the adnexa is broad and includes benign and malignant processes, as well as masses from other sites such as the uterus, gastrointestinal tract, genitourinary tract, or

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retroperitoneum. The risk of malignancy increases with patient age and with a strong family history of breast or ovarian cancer. (See Appendix 3, Risk Factors for Ovarian Cancer.) Features that help stratify the risk of malignancy and therefore guide management can be divided into patient characteristics, physical examination findings, imaging results, and serum tumor marker levels.

Patient Characteristics

A thorough personal medical and gynecologic history, family history, and review of symptoms is an important starting point. A patient’s menopausal status influences the likelihood of malignancy, as ovarian cancer is much more common in postmenopausal patients. Women in the reproductive age range may also have hemorrhagic cysts or ovarian torsion; pain that is acute in onset and then improves or that worsens acutely may be suggestive of these processes. Ovarian cancer is often associated with vague symptoms, such as abdominal bloating, generalized pain, early satiety, and increased abdominal girth. A survey of 5,012 women whose symptoms triggered diagnostic evaluation found a low rate of identification of cancer and a low rate of surgery, with surgical procedures performed in only 0.08% of patients solely as a result of participation in the study.

NCCN’s guidelines recommend a workup for patients with a suspicious or palpable pelvic mass on abdominal or pelvic examination; ascites; abdominal distention; symptoms without a source of malignancy, such as bloating, pelvic or abdominal pain, difficulty eating, or feeling full quickly; or urinary symptoms, such as urgency or frequency.

Physical Examination

As with most examinations, an evaluation of vital signs and general appearance of the patient is a good starting point. A thorough physical examination should include palpation of cervical, supraclavicular, axillary, and groin lymph nodes; a Burke W, Barkley J, Barrows E, Brooks R, Gesci K, Huber-Keener K, et al. Executive Summary of the Ovarian Cancer Evidence Review Conference. Obstet Gynecol 2023;142. The authors provided this information as a supplement to their article. ©2023 The Authors.
pulmonary examination; palpation and auscultation of the abdomen; and a pelvic examination with visual inspection of
the perineum, cervix, and vagina, as well as a bimanual examination that includes a rectovaginal examination if
indicated. Masses that are irregular, firm, fixed, nodular, bilateral, or associated with ascites are more concerning for
malignancy. Endometriosis, chronic pelvic infections, hemorrhagic cysts, tubo-ovarian abscesses, and uterine
leiomyomas may sometimes mimic these findings.¹

**Imaging**

Transvaginal ultrasonography is the most commonly used and typically most appropriate initial imaging modality for the
assessment of adnexal masses given its widespread availability, good patient tolerability, and cost effectiveness.
Ultrasonography should assess features of a mass, including the size and composition (cystic, solid, or mixed), laterality,
and the presence or absence of septations, mural nodularity, papillary excrescences, or free fluid. Doppler
ultrasonography may be helpful to evaluate for vascularity. Abdominal ultrasonography may be useful in patients with
large masses extending above the pelvis or when the ovaries are pulled cephalad as a result of prior surgery or other
conditions. The main limitations of ultrasonography are its low specificity and low positive predictive value for the
detection of cancer, especially in premenopausal women. Features seen on ultrasonography that are concerning for
malignancy include a cyst or mass greater than 10 cm in size, papillary or solid components, irregularity, presence of
ascites, and high color Doppler flow. Simple cysts are almost always benign, even in postmenopausal patients. Different
ultrasound scoring systems have been evaluated in the research setting, although none have been validated or applied
to routine clinical practice.¹

Magnetic resonance imaging (MRI) may be helpful to further distinguish benign from malignant masses, especially if
they are indeterminate with ultrasonography, and may help establish the origin if it is not clear whether a mass is arising
from the adnexa or a nearby structure.⁴ Diffusion-weighted MRI and perfusion-weighted MRI have better accuracy in
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distinguishing benign from malignant adnexal lesions compared with conventional MRI alone, with an accuracy of 95% for the combined technique. Computed tomography (CT) is useful to assess for the extent of metastatic disease, evaluate for a potential other primary site, and plan for surgery.\(^1\)

Preoperative MRI-based approaches have also been evaluated and compared with postoperative diagnoses. Although NCCN recommends ultrasonography and MRI as options for preoperative imaging, the NCCN guidelines are silent regarding the techniques to be used and do not endorse any specific model for preoperative triage.\(^3\)

For patients with a suspicious or palpable pelvic mass or concerning symptoms, NCCN’s recommended workup includes first abdominal and pelvic examination, with ultrasonography or abdominal or pelvic CT or MRI, or a combination of these, as clinically indicated. Ultrasonography has proven effective for triaging most adnexal masses as either benign or malignant and is therefore typically used for initial evaluation.\(^3\) Additional imaging may be indicated if ultrasound findings are indeterminate regarding the likelihood of malignancy or organ of origin; it may also be indicated to assess for metastatic disease or for surgical planning.\(^3\) NCCN guidelines suggest CT with oral and intravenous contrast unless contraindicated, although some practitioners omit oral contrast. Positron emission tomography (PET), CT, or MRI may be indicated if lesions are indeterminate or if the findings may alter management (ie, influence decisions about surgery vs chemotherapy or palliative care in the setting of metastatic disease). Integrated fluorodeoxyglucose (FDG) PET with CT has a higher accuracy than CT for detection of metastases and therefore may be useful if CT results are indeterminate.\(^3\) Integrated FDG PET with CT has relatively limited test characteristics to distinguish benign from malignant adnexal masses, with a sensitivity of 58% and specificity of 76%, but it has a role in evaluating for other sites of metastatic disease.\(^4\)


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Although there is no direct evidence for its necessity, chest CT or chest X-ray is recommended by NCCN as clinically indicated, based on suspicion for malignancy. Chest CT is preferred if there is concern for metastatic or widely disseminated disease, as it may detect pleural-based or pulmonary metastases. Referral to a gynecologic oncologist is recommended for clinically suspicious lesions.³

The American College of Radiology created guidelines for appropriate imaging of clinically suspected adnexal masses with no acute symptoms, in response to the fact that only 33% of women with an eventual diagnosis of ovarian cancer are referred to a gynecologic oncologist for initial management.⁴ These guidelines are consistent with those of ACOG and NCCN and are broken down into classes based on menopausal status and concern for malignancy, among others (see Appendix 6, Early Diagnosis of Ovarian Cancer).

**Laboratory Studies and Biomarkers**

Baseline blood tests should include a complete blood count and chemistry profile with liver function test. NCCN recommends evaluating the performance and nutritional status of each patient, which will drive decisions about therapy.³ Patients with poor nutritional status have higher risks of suboptimal cytoreduction, surgical complications, and worse survival, especially when elderly.³ These patients may be better served with neoadjuvant chemotherapy unless they are otherwise surgically fit and being hindered by a surgically resectable mass that inhibits gastrointestinal or other function. Nutritional status may be assessed by evaluating body weight, body mass index, anthropometrics, serum protein, serum albumin, transferrin, lymphocyte count, bioelectrical impedance, body composition measures such as adipose and lean tissue, and skeletal muscle index. The prognostic nutritional index and subjective global assessment have been used as metrics.³
Serum markers are a useful adjunct to imaging to stratify the likelihood of malignancy. Cancer antigen (CA) 125 is a glycoprotein that is often associated with ovarian cancer, especially nonmucinous epithelial malignancies. CA 125 is elevated in approximately 80% of patients with metastatic disease, but in only 50% of patients with stage I disease confined to the ovary. It can also be elevated in many other conditions and those that cause inflammation of the peritoneum, including endometriosis, pregnancy, pelvic inflammatory disease, nongynecologic malignancies, heart failure, and liver failure. As a result, the overall ability of CA 125 assessment to differentiate benign from malignant adnexal masses has wide ranges, with a sensitivity of 61% to 90%, specificity of 71% to 93%, positive predictive value of 35% to 91%, and negative predictive value of 67% to 90%, with the latter two dependent on the population evaluated.

Serum tumor marker assessment varies depending on the histology of the underlying cancer. Assessment of CA 125 is typically recommended, as it is the most common and is a standard marker for epithelial ovarian malignancies. Serum CA 125 may correlate with the extent of disease, have prognostic value, help with treatment planning, and be monitored for disease response and recurrence if malignancy is found. Therefore, knowing the baseline level is important. An elevated CA 125 level and a pelvic mass, especially in a postmenopausal woman, is very concerning for malignancy. Prior guidance from ACOG used a CA 125 threshold of more than 200 units/mL as a criterion for referral of premenopausal women to a gynecologic oncologist. This guidance, however, was based on expert opinion, and no evidence-based threshold is currently available to serve as strict criteria for referral. ACOG states, “[P]roviders should integrate the CA 125 level with other clinical factors in judging the need for consultation.” Human epididymis protein 4 (HE4) may be a prognostic marker and may be followed for treatment response and recurrence, especially in patients without CA 125 elevation at baseline. Because results vary across studies, NCCN does not currently recommend HE4 as part of the routine preoperative workup for an indeterminate adnexal mass.
Other markers may include carcinoembryonic antigen (for mucinous tumors), CA 19-9 (for mucinous tumors or those with elevations prior to surgery), and inhibin-B (for granulosa cell tumors). Malignant germ cell tumor markers include β-hCG for choriocarcinoma, alpha fetoprotein for yolk sac or endodermal sinus tumors, and lactate dehydrogenase for dysgerminoma. Germ cell tumors are more common in younger women (in their teens to their 20s) with solid adnexal masses.1

**Other Considerations**

A gastrointestinal evaluation is also recommended as clinically indicated. Patients with a strong family history of gastrointestinal malignancy or elevated carcinoembryonic antigen level may benefit from preoperative endoscopy or colon screening to rule out an occult metastasis from the gastrointestinal tract. A serum CA 125-to-carcinoembryonic antigen ratio higher than 25 has been used in clinical trials as a threshold that is more likely indicative of a gynecologic malignancy.³ Imaging demonstrating a pancreatic mass with widespread abdominal disease may also be indicative of a primary gastrointestinal malignancy.¹

NCCN also recommends obtaining a family history and referring appropriate candidates for genetic evaluation. These steps are essential, as identification of patients with mutations may inform future treatment, help to assess concurrent cancer risk, and identify family members who may benefit from screening. Moreover, patients with germline or somatic BRCA1 or BRCA2 mutations benefit from poly ADP ribose polymerase (PARP) inhibitor maintenance after initial therapy.³ More specific recommendations about genetic testing can be found in Appendix 5, Ovarian Cancer Screening; NCCN’s “Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic”; and NCCN’s “Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.” (NCCN guidelines are available at www.NCCN.org.)
**Differentiation Between Benign and Malignant Masses**

Multiple prediction algorithms incorporating factors such as symptoms, imaging results, biomarkers, and patient characteristics have been evaluated to determine which patients with an indeterminate adnexal mass are at higher risk of malignancy, need surgery (or may avoid the risk), and should be referred to a gynecologic oncologist. For example, the Risk of Ovarian Malignancy Algorithm (ROMA) uses CA 125, HE4, and menopausal status. In a 531-patient cohort, this algorithm correctly classified 93.8% of epithelial ovarian cancer cases as high risk preoperatively. In postmenopausal women, the specificity was 75% (95% confidence interval [CI] 66.9–81.4), and the sensitivity was 92.3% (95% CI 85.9–96.4). However, in premenopausal women, the specificity was 74.8% (95% CI 68.2–80.6), and the sensitivity was 76.5% (95% CI 58.8–89.3). When compared to initial clinical risk assessment by a generalist in 461 women, the ROMA performed better and detected an additional 13 malignancies that clinical assessment did not. Adding the ROMA to clinical assessment increased sensitivity by 8.4% to 93.8%, with a specificity of 67.2% and a negative predictive value of 98.8% for the detection of ovarian cancer.

The International Ovarian Tumor Analysis (IOTA) group’s Logistic Regression model 2 includes patient age and five ultrasound variables. Pooled data found a sensitivity of 0.92 (95% CI 0.88–0.95) and specificity of 0.83 (95% CI 0.77–0.88). IOTA’s Simple Rules model evaluates five features indicative of malignancy and five indicative of benign masses. It has a pooled sensitivity of 0.93 (95% CI 0.89–0.95) and specificity of 0.81 (95% CI 0.76–0.85). The IOTA Assessment of Different Neoplasias in the Adnexa (ADNEX) model combines patient age, type of center (oncology referral vs other), serum CA 125 levels, and six ultrasound variables.

The Risk of Malignancy Indexes (RMI I–IV) use ultrasound features (with a score of 0 to 3 assigned based on ultrasound findings), patient menopausal status, and serum CA 125 levels. An RMI score above 200 has been associated with a pooled sensitivity of 78% and specificity of 87% for the detection of cancer.
Some investigators have proposed combining symptom index scores with assessment of CA 125 and HE4 levels. Early ACOG guidelines (since withdrawn) suggested using patient age, CA 125 level, physical findings, imaging results, and family history.

Multiple ultrasound-based imaging algorithms have been developed and tested against surgical diagnoses. The most thoroughly evaluated algorithm is the IOTA Simple Rules algorithm, which is based on five ultrasound features to predict malignancy (vs five features to predict benign masses), and the IOTA Logistic Regression model 2, which combines five ultrasound variables with patient age.

The multivariate index assay incorporates serum levels of the biomarkers transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin, and CA 125. Miller et al sought to compare the multivariate index assay for assessing the risk of malignancy of ovarian tumors before surgery with then-current ACOG guidelines on referral (since withdrawn). The older ACOG guidelines included as part of risk assessment a family history of one or more first-degree relatives with ovarian or breast cancer for all patients. For premenopausal women, the very elevated CA 125 threshold for referral was defined as 200 units/mL; for postmenopausal women, any elevation greater than 35 units/mL was considered grounds for referral. When Miller et al conducted a prospective multi-institutional evaluation of 516 women, using the multivariate index assay in place of CA 125 findings, they found that sensitivity increased (77%–94%) and negative predictive value increased (87%–93%), while specificity decreased (68%–35%), and positive predictive value decreased (52%–40%).

Burke W, Barkley J, Barrows E, Brooks R, Gesci K, Huber-Keener K, et al. Executive Summary of the Ovarian Cancer Evidence Review Conference. Obstet Gynecol 2023;142. The authors provided this information as a supplement to their article. ©2023 The Authors.
The second-generation multivariate index assay incorporates CA 125, transferrin, apolipoprotein A1, follicle stimulating hormone, and HE4. The US Food and Drug Administration has approved the ROMA and both multivariate index assays for use in patients over age 18 with an adnexal mass for which surgery is already planned, but for whom the decision about referral to a gynecologic oncologist has not yet been made. ACOG states, “These biomarker panels are not recommended for use in the initial evaluation of an adnexal mass, but may be helpful in assessing which women would benefit from referral to a gynecologic oncologist.”\cite{1} NCCN “does not recommend the use of these biomarker tests for determining the status of an undiagnosed adnexal/pelvic mass.”\cite{3}

One meta-analysis from the United Kingdom evaluated the clinical and cost effectiveness of risk scores to guide decisions for referring women with suspected ovarian cancer to secondary care; it included 51 diagnostic cohort studies published through 2016.\cite{11} The ROMA yielded disproportionately high false-negative results in patients with borderline tumors and nongynecologic malignancies. The ADNEX model and IOTA Simple Rules approach were associated with increased sensitivity compared to current practice, resulting in the referral of more patients with malignant tumors, but also more with benign processes. The cost-effectiveness model supported prioritization of sensitivity over specificity.\cite{11}

In a cohort of 360 women scheduled for surgery, the IOTA Logistic Regression model 2 performed better (area under the curve 0.952, 94% sensitivity, 82% specificity) than the ROMA (area under the curve 0.893, 84% sensitivity, 80% specificity), suggesting that good-quality ultrasonography may be more important than HE4 and CA 125.\cite{12}

The NCCN does not endorse any of these methods:

Because the primary assessment and debulking by a gynecologic oncologist is associated with improved survival, all patients with lesions suspected to be ovarian malignancies (based on clinical evidence) should be referred to...
an experienced gynecologic oncologist for evaluation—both to assess for suitability for different primary surgical options and to select the best method for obtaining the material needed for definitive diagnosis. A gynecologic oncologist should be involved in assessing whether a patient is a suitable surgical candidate and/or an appropriate candidate for neoadjuvant therapy, and consideration of laparoscopic evaluation to determine feasibility of debulking surgery.3(pMS13)

The UK-based NICE makes a similar statement:

There is currently not enough evidence to recommend the routine adoption of the IOTA ADNEX model, [second-generation multivariate index assay], RMI I (at thresholds other than 200 or 250), ROMA or IOTA Simple Rules in secondary care in the [National Health Service] to help decide whether to refer people with suspected ovarian cancer to a specialist multidisciplinary team. The NICE guideline on ovarian cancer recommends that people with a RMI I of 250 or more are referred to a specialist [multidisciplinary team]. Evidence suggests that there is no substantial change in accuracy if the threshold for RMI is lowered to 200. ... Further research is needed on other models to determine the accuracy and impact of these methods for clinical decision making.13(p4)

Criteria for Referral to a Gynecologic Oncologist

NCCN recommends evaluation by a gynecologic oncologist for all patients with suspected ovarian malignancies.3 Data demonstrate that primary assessment and surgical debulking by a gynecologic oncologist is associated with a survival advantage. Patients who are poor surgical candidates also benefit from evaluation prior to initiation of neoadjuvant chemotherapy, especially because the decision making is nuanced. Furthermore, laparoscopic evaluation to determine feasibility of debulking surgery in select patients may be considered.3

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ACOG recommends either consultation with or referral to a gynecologic oncologist for women with an adnexal mass who meet one or more of the following criteria:\(^{1(p 	ext{e}216-e217)}\)

- Postmenopausal with elevated CA 125 level, ultrasound finding suggestive of malignancy, ascites, a nodular or fixed pelvic mass, or evidence of abdominal or distant metastasis
- Premenopausal with a very elevated CA 125 level, ultrasound findings suggestive of malignancy, ascites, a nodular or fixed pelvic mass, or evidence of abdominal or distant metastasis
- Premenopausal or postmenopausal with elevated score on a formal risk assessment test such as the multivariate index assay, risk of malignancy index, or the ROMA or one of the ultrasound-based scoring systems from the International Ovarian Tumor Analysis group

Although not specifically described in the current referral criteria but mentioned in the prior version, with the increased awareness of the genetic underpinnings for ovarian cancer, it would be reasonable to consider personal and family history in the criteria for involvement of a gynecologic oncologist.

Joint clinical practice guidelines from the Society of Gynecologic Oncology of Canada and the Society of Obstetricians and Gynaecologists of Canada recommend prompt referral to a gynecologic oncologist for any patient who presents with a mass with any of the following features suggestive of malignancy: solid component with strong or central color flow, four or more papillary projections (defined as >3 mm in height), thick multiple irregular septations, or ascites and peritoneal nodularity.\(^{14}\)

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Multiple studies have demonstrated that having a gynecologic oncologist involved in the care of ovarian cancer patients increases survival and offers other advantages. One systematic review of 18 articles published between 1991 and 2006 evaluated the relationship between care setting (type of gynecologist or hospital) and outcomes. Staging and debulking were consistently performed more adequately by gynecologic oncologists (pooled relative risk to <2 cm 1.4, 95% CI 1.2–1.5, and to no macroscopic disease 2.3, 95% CI 1.5–3.5). No differences were found in complication rates. Chemotherapy was given from 1% to 15% more often in specialized settings. Long-term survival was improved after treatment in a specialized hospital, and surgery by a gynecologic oncologist resulted in improved survival in patients, with a 5–8-month median survival benefit for patients with advanced disease.

Evaluation of 31,897 patients with stage IIIIC or IV ovarian cancer using four state cancer registries demonstrated that patients treated by a general surgeon had a higher likelihood of an ostomy (odds ratio 4.46, \(P < .0001\)) and a higher risk of death (hazard ratio [HR] 1.63, \(P < .0001\)) than those treated by a gynecologic oncologist. Other data have shown that women treated by a gynecologic oncologist were more likely to undergo primary staging surgery, were more likely to receive chemotherapy, and had improved survival (38.6% vs 30.3%, \(P < .001\)) compared with those treated by other providers. A study using the National Cancer Institute’s Surveillance, Epidemiology, and End Results program database that evaluated 11,688 ovarian cancer patients also demonstrated that women receiving surgery from a gynecologic oncologist vs a nongynecologic oncologist were 2.35 times more likely to receive the surgical standard of care and 1.25 times more likely to receive the chemotherapeutic standard of care. Median survival was 14 months longer for patients receiving the standard of care, though individual patient and other factors also may have contributed to survival.

A single-institution review found that adherence to NCCN’s guidelines for workup for ovarian cancer patients, including tumor marker testing, resulted in shortened times to referral to a gynecologic oncologist and also minimized cost.
inefficiency and delays. These results are consistent with older data, including a 2006 evaluation of Medicare claims that demonstrated that among patients with stage I–II ovarian cancer, those undergoing surgery by a gynecologic oncologist were more likely to have a lymph node dissection compared with those undergoing surgery by a general gynecologist or general surgeon (60% vs 36% vs 26%). In patients with stage III–IV disease, those undergoing surgery by a gynecologic oncologist were more likely to have a debulking procedure than those undergoing surgery by a general gynecologist or general surgeon (58% vs 51% vs 40%, \( P < .001 \)) and more likely to receive postoperative chemotherapy when operated on by a gynecologic oncologist or a general gynecologist than by a general surgeon (79% vs 76% vs 72%, \( P < .001 \)). Survival was also better among patients operated on by a gynecologic oncologist than by a general gynecologist (HR 0.85, 95% CI 0.76–0.95) or general surgeon (HR 0.86, 95% CI 0.78–0.96).

The American Society of Clinical Oncology created resource-stratified guidelines for the assessment of adult women with ovarian masses and the treatment of ovarian cancer to provide guidance for providers in resource-constrained settings. The guidelines state, “Ovarian cancer surgery should be performed by trained gynecologic oncologists or surgeons with oncology surgical expertise. ... Where feasible, patients with presumed early-stage ovarian cancer should undergo surgical staging by trained surgeon(s).”

Evaluation by a gynecologic oncologist is also recommended for patients with occult serous tubal intraepithelial carcinoma. Patients with a previous diagnosis of ovarian cancer confirmed by surgery, cytology, or tissue biopsy should be referred to a gynecologic oncologist. Further discussion of this is beyond the scope of this review.

A multidisciplinary approach to ovarian cancer care is important and improves quality of care. Advanced care providers, expert nurses, nurse navigators, social workers, and others who offer supportive care all play a role.
What Is the Usual Trajectory after Referral to a Gynecologic Oncologist?

Management decisions for patients with ovarian cancer have important, complex, and subtle nuances that must be carefully considered. Clinical scenarios vary substantially, making it difficult to apply guidelines to management uniformly.

Principles of Surgery

NCCN describes primary treatment based on assessment of presumed clinical stage and the desire to preserve fertility. For patients with ovary-confined disease who desire future fertility, removal of the affected ovary (for stage IA) or both ovaries (for stage IB) with preservation of the uterus and comprehensive surgical staging is a reasonable primary consideration (see Box 1). Most data supporting this approach come from small single- or multi-institution studies; although data are limited, they do not show an increased risk of recurrence with this approach.23,24 Patient counseling by a gynecologic oncologist is appropriate, as risks of occult disease in the other ovary or recurrence may be increased. Referral to a fertility specialist is also recommended.3
Box 1. Comprehensive Surgical Staging*

- Thorough abdominal exploration, aspirating ascites or obtaining pelvic washings
- Biopsy of any suspicious areas or adhesions, otherwise performing random peritoneal biopsies from the pelvis, paracolic gutters, and undersurface of the diaphragm (vs diaphragm cytology)
- Omentectomy
- Pelvic lymph node dissection with bilateral removal of the lymph nodes overlying and anterolateral to the common iliac vessel, overlying and medial to the external iliac vessel, overlying and medial to the hypogastric or internal iliac vessels, and from the obturator fossa at a minimum anterior to the obturator nerve†
- Para-aortic lymph nodes dissection with stripping of the nodal tissue from the vena cava and aorta bilaterally to at least the level of the inferior mesenteric artery and preferably to the level to the renal vessels‡

https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf†Staging
Fertility-sparing surgery may also be an option for some patients with stage IC disease (positive abdominal or pelvic cytology, capsular involvement, or intraoperative rupture) depending on histology, and a balanced discussion of the risks and benefits of this approach is needed, especially in patients with capsular involvement or ascites on entry who may be at higher risk with fertility-sparing approaches. For patients who do not desire a fertility-sparing approach and who do not have obvious metastatic disease, hysterectomy with bilateral salpingo-oophorectomy and comprehensive surgical staging is recommended. (See Appendix 8, Special Considerations, for additional details.)

The decision to undergo neoadjuvant chemotherapy vs primary surgical tumor debulking is a complex, nuanced one with many layers and much controversy. The Society of Gynecologic Oncology and the American Society of Clinical Oncology convened an expert panel and conducted a systematic review of the literature, with results published in 2016 in leading gynecologic oncology and clinical oncology journals. Four phase III clinical trials were the primary evidence base. The expert panel concluded that all women with advanced (stage IIIC or IV) ovarian cancer should be evaluated by a gynecologic oncologist prior to initiation of therapy, with the preferred primary clinical evaluation consisting of CT of the chest, abdomen, and pelvis. For women with a high perioperative risk profile or a low likelihood of achieving cytoreduction to less than 1 cm of residual disease, neoadjuvant chemotherapy should be administered. Women who are fit for primary cytoreductive surgery, with potentially resectable disease, may receive either neoadjuvant chemotherapy or primary cytoreductive surgery, though primary surgery is recommended if the likelihood of optimal cytoreduction is high and morbidity is acceptable. All patients should have histopathologic or cytologic confirmation of primary site prior to initiation of neoadjuvant chemotherapy.

For patients who are surgical candidates who have metastatic disease that is surgically resectable, surgical debulking is recommended. For patients who are poor surgical candidates or in whom the likelihood of a complete surgical Burke W, Barkley J, Barrows E, Brooks R, Gesci K, Huber-Keener K, et al. Executive Summary of the Ovarian Cancer Evidence Review Conference. Obstet Gynecol 2023;142.
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cytoreduction is low, neoadjuvant chemotherapy may be appropriate.\textsuperscript{3,27} Evaluation by a gynecologic oncologist is recommended to make this decision, prior to initiation of neoadjuvant chemotherapy.

NCCN recommends that surgery be performed by a gynecologic oncologist.\textsuperscript{3} ACOG also recommends that a physician trained to appropriately stage and debulk ovarian cancer should perform the operation when a patient with a suspicious or persistent complex adnexal mass requires surgical evaluation, and that when a malignant ovarian tumor is discovered incidentally, a gynecologic oncologist should be consulted intraoperatively if possible.\textsuperscript{1} NCCN guidelines state that an exploratory laparotomy through an open midline vertical incision should be used in most patients with suspected ovarian, fallopian tube, or primary peritoneal cancer in whom surgical staging or primary, interval, or secondary surgical debulking is planned. For select patients with early-stage disease, a minimally invasive surgical approach may be employed by an experienced surgeon.\textsuperscript{1} Laparoscopy may be considered when there is no risk of spillage or when the mass has already been removed.\textsuperscript{25}

Laparoscopy can also be a useful tool to evaluate the feasibility of optimal cytoreduction in patients with newly diagnosed advanced-stage disease or recurrent disease.\textsuperscript{28} Minimally invasive surgery may also be used in select patients for interval debulking procedures. However, in patients in whom minimally invasive surgery will not result in optimal debulking, conversion to an open procedure should be considered.

In general, every effort should be made with surgery to evaluate for occult disease in the upper abdomen or retroperitoneum that might otherwise be missed and to remove all gross visible disease that is found. Although residual disease of less than 1 cm has historically been defined as optimal cytoreduction, maximal effort should be made to remove all gross disease, as this is clearly associated with improved survival outcomes.\textsuperscript{29} Suspicious or enlarged lymph...
nodes identified on preoperative imaging or surgical exploration should be removed. However, empiric complete lymphadenectomy in the absence of visible disease is not required, as it has not been uniformly associated with survival benefits. Placement of an intraperitoneal port for adjuvant chemotherapy administration may be considered for select candidates in whom optimal tumor debulking has been accomplished.

Given the widespread peritoneal dissemination of ovarian cancer, surgical cytoreduction (or tumor debulking) procedures can be very extensive to remove all visible disease. These procedures may include bowel resection, appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy, ureteroneocystostomy, partial heptectomy, partial gastrectomy, cholecystectomy, and distal pancreatectomy. Thus, extensive debulking is associated with significant perioperative risk and morbidity. Therefore, patient factors such as functional and nutritional status, patient goals, shared decision-making, and the clinical judgement of the gynecologic oncologist are important considerations when deciding who are appropriate candidates for these procedures given the increased risks.

**Systemic Treatment**

Whenever possible, health care professionals should consider referring patients with ovarian cancer to clinical trials. In general, adjuvant chemotherapy is recommended for most patients with ovarian cancer, with the exception of patients with low-grade (ie, grade 1; grade 2 is controversial) stage IA/B ovarian cancer and patients with select histologies. Adjuvant chemotherapy for epithelial cancer typically consists of intravenous carboplatin and paclitaxel. Determining the optimal number of cycles, dosing, and frequency of chemotherapy is complex, so counseling by a gynecologic oncologist is important. Incorporation of bevacizumab and PARP inhibitor maintenance may be considered in advanced disease. Combination intravenous intraperitoneal chemotherapy with cisplatin and paclitaxel may also be considered in
select candidates with gross residual disease of less than 1 cm (ie, optimal cytoreduction). For patients with malignant germ cell tumors stage IC and higher, bleomycin, etoposide, and cisplatin may be considered.

**Genetic Counseling**

Patients with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer should also have genetic risk evaluation and germline and somatic testing if they have not already. Appendix 5, Ovarian Cancer Screening, discusses genetic counseling. Facilitated referral to genetic counseling using mechanisms such as patient navigators has been shown to be an effective strategy with a high uptake of genetic counseling and testing, without causing psychologic harm. Factors that have been shown to be associated with decreased referral rates include older age, living more than 100 miles from the treating center, and death within 1 year of initiating treatment. Both germline (blood or buccal) and somatic (tumor) testing should be performed.

**Role of the Primary Care Provider**

Because most patients with ovarian cancer will undergo surgery and chemotherapy at some point, the primary care provider can play an important role in optimizing the status of the patient to undergo such treatment. Frailty is an indicator of poor outcomes in patients with ovarian cancer, thus all efforts to improve the patient’s functional status and nutrition and to minimize the treatment-related risks from medical problems (eg, diabetes and cardiac disease) are beneficial.

**DISCUSSION**
A thorough clinical evaluation at presentation is essential to stratify the likelihood of malignancy. For these patients, the recommended workup includes first an abdominal or pelvic examination, followed by ultrasonography or abdominal or pelvic CT or MRI as clinically indicated. For most adnexal masses, ultrasonography is effective for determining whether the mass is benign or malignant and is therefore typically used for initial evaluation. Additional imaging may be indicated if ultrasound findings are indeterminate as to the likelihood of malignancy or organ of origin to assess for metastatic disease and for surgical planning. Serum tumor marker assessment, most notably CA 125, is also important to serve as a baseline and help determine which patients should be referred to a gynecologic oncologist.

Different societies have described different referral guidelines. In short, if there is any concern for a possible malignancy, referral to a gynecologic oncologist is warranted. Survival and other outcomes are improved when patients with ovarian cancer have a gynecologic oncologist involved in their care.

Strengths of this Review

- Multiple societies have generated recent reviews, guidelines, and statements about ovarian cancer.
- Many modalities exist to distinguish a benign from a malignant adnexal mass.

Weaknesses of this Review

- Modern diagnostic tests have limited capacity to detect ovarian cancer at an early stage.
- Although multiple algorithms—including combinations of imaging, patient factors, and serum values—have been designed, there is no clear evidence or uniform guidelines about which is superior.
- Most guidelines are relatively vague, leaving much up to the discretion of the referring provider.
Gaps in the Literature

- Guidelines for referral are somewhat vague.
- Patterns for referral are still not standardized. Many ovarian patients are not referred to or do not receive care by a gynecologic oncologist, highlighting an educational need. Minimal research exists to explain why patients with ovarian cancer are not being seen by a gynecologic oncologist.
- Although multiple algorithms exist, there is no clear consensus about the utility or benefit of one over another.
- Interventions to promote early presentation and referral for patients with ovarian cancer are lacking and ineffective.
- There is clear opportunity to improve referrals and access to gynecologic oncology specialty care for patients with ovarian cancer, and the primary care provider is central to this process.

REFERENCES


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INTRODUCTION

This document addresses the various special considerations that primary care practitioners should be aware of regarding the ovarian cancer continuum. The literature search for this document paid special attention to approaches for fertility preservation in young patients with an ovarian cancer diagnosis as well as patients at high risk for developing ovarian cancer. Additionally, the effects of ovarian cancer history on quality of life, sexual health, and psychosocial issues were explored. Menopause symptom management and contraception were addressed.

METHODS

The American College of Obstetricians and Gynecologists’ (ACOG’s) Resource Center searched the Cochrane, MEDLINE through Ovid, and PubMed databases using a search strategy based on the topics of interest described. Results were categorized according to the following levels of evidence:

- Level I: Randomized controlled trials (RCTs), systematic reviews, and meta-analyses
- Level II: Observational studies
• Level III: Guidelines and narrative reviews
• No level: References that were not fully indexed by level at the time of the literature search

Additional relevant guidelines were identified and sorted by relevance. Guidelines were specifically sought from ACOG, the American College of Radiology, the American Society for Reproductive Medicine, the European Society for Medical Oncology, the National Comprehensive Cancer Network (NCCN), the National Institute for Health and Care Excellence, the Royal College of Obstetricians and Gynaecologists, the Society of Gynecologic Oncology, the Society of Obstetricians and Gynaecologists of Canada, and the US Preventive Services Task Force. A single investigator reviewed the titles and abstracts of all collected articles and guidelines. Selected manuscripts were then reviewed in full.

Inclusion criteria were major professional society and health service guidelines, systematic reviews, meta-analyses, RCTs, cohort studies, and case–control studies available in English and published between 2000 and 2021. Articles were excluded if they were case reports, case series, were unavailable in English, or were from countries not in the very high category of the United Nations Human Development Index.

Priority was given to systematic reviews and meta-analyses, and individual studies included in them were generally not reviewed separately unless they contained additional pertinent information not otherwise found in the systematic review. Nonsystematic review articles were generally excluded except when high-quality studies could not be found for a specific topic. Reference lists of nonsystematic reviews were evaluated for relevant papers that might have been missed by the literature search.

RESULTS

Burke W, Barkley J, Barrows E, Brooks R, Gesci K, Huber-Keener K, et al. Executive Summary of the Ovarian Cancer Evidence Review Conference. Obstet Gynecol 2023;142. The authors provided this information as a supplement to their article.
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Literature Summary

The initial literature review identified 746 studies pertaining to the designated topics. It located 22 level I RCTs, all of which were reviewed and excluded, as they were either very small studies or did not fulfill the search or eligibility criteria. A total of 23 level 1 meta-analyses or systematic reviews were found, and, after review, seven were included. The studies excluded did not fulfill the eligibility criteria or answer the relevant questions. Of the 260 level II studies reviewed, five were included and the remainder excluded. The 85 level III studies were all reviewed and excluded. Of the 188 studies without an associated level, all were reviewed and two were included. The 64 assorted studies from PubMed (all levels) were reviewed, and three were included. Another 74 studies from PubMed without a designated evidence level were reviewed and excluded. Finally, 31 publications from various governing bodies were reviewed, and 10 were included. The primary reviewer independently identified 14 additional papers via PubMed that were included. A total of 41 publications were included in the final review.

Summary of Data

Fertility-Sparing Surgeries

Although epithelial ovarian cancer most frequently presents well after menopause and at an advanced disease stage, 12% of cases occur in women under 45 years of age, in whom ovarian cancer is more likely to present at an earlier stage. In these women it is appropriate to consider avoiding the traditional radical surgical approach of a hysterectomy, bilateral salpingo-oophorectomy (BSO), and comprehensive surgical staging in an effort to preserve future fertility. The alternative approach, referred to as fertility-sparing surgery, typically consists of a unilateral salpingo-oophorectomy and surgical staging, thereby allowing for retention of the unaffected ovary and uterus.
Substantiating the utility of this approach, Bentivegna et al performed a systematic review of 39 case series analyzing a total of 1,150 patients who underwent fertility-sparing surgery in the setting of various stages, grades, and histologies of ovarian cancers. Recurrences occurred in 10% of patients with stage 1A disease (7% of IA1 disease, 11% of IA2, and 29% of IA3, \( P = .0004 \)), and 16% of patients with stage 1C (11%, 11%, and 23% for stages IC1, IC2, and IC3 respectively, \( P = .02 \)).\(^2\) Bercow et al performed a systematic review of 117 studies to assess the effect of fertility-sparing surgery on the reproductive and oncologic outcome in patients with ovarian cancer, and they found the recurrence rate after fertility-sparing surgery for early-stage ovarian cancer ranged from 5% to 18%.\(^3\) Another group, Melamed et al, performed a population-based study using data from 1,726 patients in the National Cancer Database with stage IA and unilateral stage IC epithelial ovarian cancer and found that survival for women 5 years after fertility-sparing surgery was 93.5%, compared with 90.5% after conventional surgery, while after 10 years, survival was 88.5% and 88.9%, respectively.\(^4\) Crafton et al additionally performed a population-based retrospective cohort study evaluating 9,017 patients from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database and the National Cancer Database and found that, when applied to stage II–IV epithelial ovarian cancers, fertility-sparing surgery is significantly associated with a lower overall survival rate than conventional surgery (hazard ratio [HR] 1.61, 95% confidence interval [CI] 1.22–2.12).\(^5\)

Approximately 1.2% of epithelial ovarian cancer patients qualify for fertility-sparing surgery, and its use varies greatly across demographics.\(^2,4\) In their cohort study using National Cancer Database patients from 2004 through 2012, Melamed et al identified 1,726 women under age 40 with stage IA and IC epithelial ovarian cancer.\(^4\) They found that women were more likely to receive fertility-sparing surgery if they were younger than 25 years old (85.2% compared with 27.5% of women over age 35), of non-White race (54.5% compared with 42.3%), or living in an urban area (50.5% compared with 31.3%), and they had serous or mucinous histology.\(^4\) Wright et al identified 1,186 patients with epithelial ovarian cancer diagnosed at age 50 or younger in the SEER database from 1988 through 2004 who had fertility-sparing
surgery; the approach was positively associated with younger age, later year at diagnosis, residence in the eastern or western United States, and histology other than clear cell or endometrioid tumors ($P < .05$).\textsuperscript{6}

Obstetric outcomes following fertility-sparing surgery typically mirror the baseline population rate. In their systematic review, Bercow et al found nine studies reporting on obstetric outcomes in epithelial ovarian cancer patients who had undergone fertility-sparing surgery treatment.\textsuperscript{3} There were 307 patients who attempted to conceive, 242 of whom were successful (79%), consistent with the lower end of generally accepted population rates of 78% to 95%.\textsuperscript{3} Morrison and Nasioudis performed a systematic review of 47 studies, including 2,189 patients, focused on patients with malignant ovarian germ cell tumors and found that approximately 80% of these patients required chemotherapy following fertility-sparing surgery, of whom 3.7% developed premature ovarian insufficiency. In the remaining patients, about 80% of women who attempted to conceive had at least one pregnancy, 77.6% had a live birth, and the preterm birth rate was only 3%.\textsuperscript{7}

Guidelines from NCCN state, “Fertility-sparing surgery may be considered for patients who wish to preserve fertility and have apparent early-stage disease and/or low-risk tumors, such as early-stage invasive epithelial tumors, [low malignant potential] lesions, malignant germ cell tumors, or malignant sex cord-stromal tumors. Even if the contralateral ovary cannot be spared, uterine preservation can be considered as it allows for potential future assisted reproductive approaches.”\textsuperscript{8(pMS19-MS20)} NCCN also recommends that patients who wish to retain fertility should be referred to a reproductive endocrinology specialist for preoperative evaluation and consultation.\textsuperscript{8}

Regarding nonepithelial ovarian cancers, the European Society for Medical Oncology recommends that fertility-sparing surgery be considered for germ cell histologies presenting in stages IA to IC and can be considered up to stage IV in


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certain cases. For granulosa cell tumors, the European Society for Medical Oncology recommends fertility-sparing surgery be offered in stage IA to IC, whereas for Sertoli-Leydig tumors, fertility-sparing surgery should be reserved for stage IA alone except in special circumstances.9 The American Society of Clinical Oncology also provides guidelines for using fertility-sparing surgery on the basis of histology, stating that fertility-sparing surgery can be considered for borderline ovarian tumors (clear cell, serous, mucinous, or endometrioid) for stage IA and IB; for mucinous carcinoma at stage IA, IB, and IC; for low-grade endometrioid carcinoma for stage IA and IB; and for low-grade serous carcinoma for stage IA and IB. The American Society of Clinical Oncology does not recommend fertility-sparing surgery for clear cell, high-grade serous, or high-grade endometrioid tumors at any stage.10

**Ovarian Cancer Effect on Quality of Life**

Patients’ assessments of quality of life following ovarian cancer treatment often show a predominantly positive outlook despite persistent symptoms. Stewart et al performed a survey of 200 women at least 2 years out from any active treatment with no known residual disease, and 89% of responders felt their current health was “good to excellent.”11 Fewer than 4% of the women needed help with their activities of daily living, and, overall, their mental health was consistent with the population norm based on the five-item Mental Health Inventory.11 Watts et al performed a meta-analysis of 24 studies, involving 3,623 patients, to assess depression and anxiety in ovarian cancer and found that after treatment the prevalence of depression was 12.71% (CI 10.14%–15.79%), decreased from 25.34% (CI 22.79%–28.07%) before treatment.12 In contrast, anxiety increased from a pretreatment rate of 19.12% (CI 17.11%–21.30%) to 27.09% (CI 23.10%–31.49%) posttreatment. These posttreatment rates of depression and anxiety were slightly higher than the baseline population prevalence of about 10% and 18%, respectively.12

Physically, patients have many residual symptoms to contend with following completion of treatment for their ovarian cancer. In their survey, Stewart et al noted that, among women who had chemotherapy, 44.5% felt they could not think
as clearly as they had before treatment, and 52% felt memory had become worse following chemotherapy exposure.\textsuperscript{11}

In their systematic review of 31 articles evaluating quality of life in ovarian cancer survivors, Ahmed-Lecheheb and Joly identified a single study regarding long-term residual neuropathic symptoms and reported that over half (51%) of the women who received chemotherapy had residual neuropathic symptoms as far as 12 years out from the end of treatment.\textsuperscript{13} Trivers et al performed a systematic review of 34 articles addressing issues affecting ovarian cancer survivors, 29 or which were quantitative in nature and included 4,822 subjects.\textsuperscript{14} They found that pain remains present in 50% or more of ovarian cancer survivors; is predominantly located in the pelvis, bladder, groin, and bowel; and does not vary based on patient age. The other most common residual symptoms are fatigue (70%), peripheral neuropathy, nausea (30%), decreased libido (30%), hair loss, and anorexia. Younger age at diagnosis was associated with better physical functioning but also made survivors more likely to report a diagnosis of hypertension, hypercholesterolemia, or hearing loss.\textsuperscript{14}

Pelvic health following treatment for ovarian cancer varies. A systematic review by Pizzoferrato et al evaluated 18 studies to describe the effect of ovarian cancer on pelvic floor disorders and sexuality and found that, following treatment for ovarian cancer, urinary incontinence and prolapse remain no different from population rates, but fecal incontinence increased from 4% preoperatively to 16% postoperatively.\textsuperscript{15} Additionally, sexuality was affected in women treated surgically for ovarian cancer, with 47% of patients reporting little or no sexual desire, 62% reporting pain with sex, and 80% reporting vaginal dryness.\textsuperscript{15} In the review by Trivers et al, multiple studies reported that the majority of women with epithelial ovarian cancer reported sexual inactivity following their treatment, and one study of 58 early-stage ovarian cancer survivors found that fewer than 10% of survivors reported either having an interest in sex or being sexually active.\textsuperscript{14} Logue et al performed a review of 29 studies containing a total of 4,116 patients with epithelial ovarian cancer and found that risk factors for worse psychosexual morbidity in women with epithelial ovarian cancer include younger age (<53 years), premenopausal status at diagnosis, chemotherapy, extent of surgery, and comorbidities,
including anxiety, depression, and cardiovascular conditions. Body image also suffers in women with epithelial ovarian cancer; between 30% and 50% of women feel less sexually attractive following their diagnosis.

The review by Trivers et al addressed financial health in addition to physical health and found that about 43% of survivors returned to work following treatment, compared with the 67% of patients who worked before their diagnosis, and many women considered their diagnosis the impetus to move into retirement. Overall socioeconomic status for patients remained unchanged across stages of diagnosis, treatment, and posttreatment. For women who returned to work, motivations included feelings of achievement and the symbolic feeling of having overcome cancer by being able to return to “normal.”

Hasenburg et al investigated the mitigating effect of fertility-sparing surgery on quality of life in patients with ovarian cancer who had malignant ovarian germ cell tumors or sex cord-stromal tumors with a multicenter cohort study of 355 patients. They found that women who underwent fertility-sparing surgery were 2.6 times more likely to be sexually active than those who underwent conventional surgical treatment ($P = .22$). Those who were sexually active reported significantly less discomfort with sex than their conventional-treatment counterparts (38% compared with 58%, adjusted odds ratio [OR] 2.8, $P = .18$). There was no difference in the two groups’ experience of pleasure during intercourse, but women who underwent fertility-sparing surgery had significantly better global quality of life (6.2 points different on a 100-point scale, $P = .03$). For women not offered fertility-sparing surgery, anger and regret were common, and some patients reported their subsequent infertility as a more traumatic condition than their original diagnosis.

A clinical practice statement from the Society of Gynecologic Oncology details methods for assessing social needs affecting quality of life among patients with gynecologic malignancies, including financial, psychological, and spiritual


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needs; issues with jobs, transportation, food, housing, and utility insecurities; and caregiver burden. The Society of Gynecologic Oncology emphasizes that “while quantification of unmet needs and effecting improvements to the care experience remain a challenge, integration of a social needs assessment tool is the first step in recognizing the potential impact social determinants of health may have in gynecologic cancer outcomes.”

**Caring for Survivors**

**Patient Concerns**

Communication between patients and physicians, while always important, is particularly key to patient satisfaction in the years following diagnosis with ovarian cancer. Many survivors report difficulty discussing their sexual concerns with their providers, reporting anxieties about causing embarrassment and using too much of their doctor’s time. The review by Trivers et al found that during recovery, 62% of survivors used at least one type of complementary therapy (including osteopathy, herbs or vitamins, acupuncture, prayer, yoga, meditation, and massage), and women reported difficulties discussing this with their physicians given the belief that their doctors do not view these treatments as valid. The review by Ahmed-Lecheheb and Joly described a study that compared patients’ study-reported symptoms with the symptoms reported in their medical visit notes and found that the patients consistently reported fewer symptoms to their doctors than on their study questionnaires. This finding was most marked when reporting psychological, hormonal, neurologic, and sexual symptoms. These findings emphasize the importance of provider-driven symptom screening questions and open communication.

**Hormone Therapy**

Many women diagnosed with ovarian cancer will undergo a BSO during their course of treatment. For premenopausal women, this procedure leads to a sudden postmenopausal state, with typical associated symptoms, including hot
flushes, night sweats, sexual dysfunction, mood and concentration changes, and sleep difficulties. Additionally, there is evidence of added morbidity following surgically induced menopause in the baseline population. This finding was demonstrated by Rocca et al, who performed a cohort study of 1,623 women who underwent bilateral oophorectomy and 1,623 age-matched referent women, none of whom had a diagnosis of ovarian cancer. They found that women who underwent oophorectomy before age 46 had a significant increased risk of subsequent multimorbidity (depression, hyperlipidemia, cardiac arrhythmias, coronary artery disease, arthritis, asthma, chronic obstructive pulmonary disease, and osteoporosis, all with HRs ranging between 1.23 and 2.08), as well as an accelerated rate of accumulation of 18 chronic conditions considered together (HR 1.22, 95% CI 1.14–1.31, P < .001).19

In average-risk patients, hormone therapy (HT) is effective for treating vasomotor symptoms (hot flushes), sexual dysfunction, and urogenital symptoms. Available data consistently show no increased risks with the use of HT for most epithelial ovarian cancer survivors, and some indicate there may be improved overall survival with the use of HT.20-22 In one study, Li et al performed a systematic review and meta-analysis of two RCTs and four cohort studies, including a total of 1,448 epithelial ovarian cancer survivors, 419 of whom used HT. When evaluated together, they found that postoperative HT use was associated with improved overall survival (aggregated HR 0.69, 95% CI 0.61–0.79); however, when the two RCTs were evaluated separately from the cohort studies, there was no longer a positive relationship (HR 1.03, 95% CI 0.58–1.83).20

A meta-analysis by Pergialiotis et al of six studies involving 1,521 ovarian cancer survivors assessed the safety of HT in women with epithelial ovarian cancer and found a 29.6% rate of HT use with no difference in disease recurrence rates related to HT (OR 0.71, 95% CI 0.45–1.14). Additionally, there was a statistically significant reduction in ovarian cancer-related deaths in the treatment group (OR 0.47, 95% CI 0.28–0.80).22 Another group, Eeles et al, performed a multicenter RCT in Europe evaluating the effect of HT on women with epithelial ovarian cancer.23 While their trial closed early due to slow accrual after only 150 of the intended 570 patients were enrolled, analysis of their data after long-term follow-up found improvement in both relapse-free and overall survival in the HT arm of the study compared with control

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subjects over the past 19 years (HR 0.67, 95% CI 0.47–0.97, \( P = .032 \), and HR 0.63, 95% CI 0.44–0.90, \( P = .011 \), respectively).  

In 2020 the Society for Gynecologic Oncology released a guideline statement endorsed by the North American Menopause Society regarding HT in the setting of ovarian cancer. The guideline states that estrogen therapy (ET) “can be prescribed for women with epithelial ovarian cancer. There is lack of data as it pertains to specific subsets of epithelial ovarian cancer, however given that low grade serous and endometrioid ovarian cancer may respond to treatment with anti-estrogen therapies HT is not recommended. There is insufficient data to make a recommendation regarding HT in women with a history of borderline tumors of the ovary.”

Guidelines from the European Society for Medical Oncology state that HT may be used safely for many germ cell tumors, but HT should be avoided for sex cord-stromal tumors, as these malignancies are thought to be hormone-dependent.

**CONTRACEPTION**

Guidelines from the Centers for Disease Control and Prevention’s Medical Eligibility Criteria for Contraceptive Use consider all contraceptives to be category 1 in the setting of ovarian cancer, meaning that there is no restriction for the use of the contraceptive method. The criteria specifically state that women who undergo fertility-sparing treatment and need contraception may use a copper or levonorgestrel intrauterine device, and that while, in general, treatment of ovarian cancer can render a woman sterile, combined and progesterone-only hormonal contraceptives are safe for use while a woman is awaiting treatment. Additionally, European Society for Medical Oncology guidelines specify that “hormonal contraception is not contraindicated for women diagnosed with [germ cell tumors] receiving fertility-sparing treatment and wanting to postpone or avoid pregnancies.”

Burke W, Barkley J, Barrows E, Brooks R, Gesci K, Huber-Keener K, et al. Executive Summary of the Ovarian Cancer Evidence Review Conference. Obstet Gynecol 2023;142. The authors provided this information as a supplement to their article. ©2023 The Authors.
Management of Women at High Risk for Ovarian Cancer

Women with multiple family members who have breast or ovarian cancer across multiple generations in their family are considered to have hereditary breast and ovarian cancer syndrome and are at high risk for developing breast and ovarian cancers.26 The primary option for reduction of cancer risk in these women is to undergo risk-reducing BSO, hereafter referred to as RRSO. RRSO provides about an 80% reduction in a patient’s risk of ovarian cancer (HR 0.21, 95% CI 0.12–0.39) as demonstrated by Rebbeck et al in their meta-analysis of three nonoverlapping datasets that included 2,840 participants.27

Another intervention that can reduce the risk of ovarian cancer in this population is the use of oral contraceptives. A meta-analysis by Iodice et al included 18 case–control and retrospective cohort studies with 1,503 ovarian cancer cases and 2,855 breast cancer cases in BRCA1 and BRCA2 mutation carriers; it found a significant risk reduction in ovarian cancer for patients who used oral contraceptives (summary relative risk [RR] 0.50, 95% CI 0.33–0.71).28 This risk reduction increased by 36% for each additional 10 years of oral contraceptive use (summary RR 0.64, 95% CI 0.53–0.78), and there was no increased risk of breast cancer in these patients (summary RR 1.13, 95% CI 0.88–1.45).

Regarding the approach to screening high-risk patients for ovarian cancer, there is the option to perform serial screenings with pelvic ultrasonography and assessment of cancer antigen (CA) 125. Unfortunately, the survival benefit of this approach remains unknown, and it is associated with high rates of false-positive results and unneeded surgery.29 In a 2017 study investigating such screening, Rosenthal et al performed a trial involving 4,348 patients with an estimated lifetime risk of ovarian cancer higher than 10%.30 They performed CA 125 testing every 4 months and did pelvic ultrasonography in an interval determined by the patient’s Risk of Ovarian Cancer Algorithm score, but no less than annually. In all, 3.7% of women screened underwent screen-positive trial surgery and, among these patients, there was a 92% false-positive rate. The positive predictive value and negative predictive value for the detection of ovarian cancer or Burke W, Barkley J, Barrows E, Brooks R, Gesci K, Huber-Keener K, et al. Executive Summary of the Ovarian Cancer Evidence Review Conference. Obstet Gynecol 2023;142.

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fallopian tube cancer 1 year into screening were 10.8% (CI 6.5%–16.5%) and 100% (CI 100%–100%), respectively.

Positive predictive value was higher in *BRCA1* and *BRCA2* carriers (42.9%) than in those with an unknown mutation status (7.7%).

Another group performed a study evaluating the use of pelvic examinations, CA 125 assessment, and pelvic ultrasonography as a screening method for 312 patients with either *BRCA1*, *BRCA2*, hereditary breast and ovarian cancer syndrome, or breast cancer from a hereditary breast cancer family and found a sensitivity, specificity, positive predictive value, and negative predictive value of 40%, 99%, 40%, and 99%, respectively. This group found three screen-detected carcinomas (one stage IC, one stage IIIb, and one stage IV), one interval carcinoma (stage IV), and five occult carcinomas at the time of RRSO following negative screening (two stage IA, one stage IC, one stage IIIb, and one stage IV). Overall there is no unified evidence showing an improvement in survival with this screening method, and, according to NCCN, such screening should be reserved for those patients who do not elect RRSO. (Appendix 6, Early Diagnosis of Ovarian Cancer, discusses screening in more detail.)

It is a challenging decision for a woman to undergo an RRSO, and not every high-risk person will choose to do so. In a systematic review by Howard et al, 43 studies (34 quantitative studies, accounting for 6,583 subjects, and nine qualitative studies with a total of 217 subjects) were assessed to evaluate the factors affecting the decision to undergo RRSO, and uptake rates for RRSO varied significantly among studies (5.4% to 78%). Patients reported reduction of anxiety and uncertainty as the reasons for proceeding with a RRSO, describing the perception of their ovaries as “time bombs” to represent their motivations. Regarding hesitation to proceed, women cited concerns about surgical menopause, acceleration of the aging process, and the need for HT. Family history of other first and second-degree relatives affected by breast and/or ovarian cancer was cited as a reason to proceed with RRSO, while family obligations were a reason to defer due to concerns about an inability to care for the family during the recovery period. Predictive

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features of women choosing RRSO included age over 40 years, parity, family history of ovarian cancer in a mother or sister, and having a confirmed positive mutation status. One prospective study by Tiller et al monitored 95 women attending a familial cancer clinic and found age was the most significant predictor of uptake of prophylactic oophorectomy, with no patients under age 35 undergoing RRSO compared with 19.6% of patients over age 35 \( (P = .009) \).

To evaluate patient choice in deciding between RRSO and periodic screenings, Westin et al performed a survey of 313 BRCA1- or BRCA2-positive patients and found that, while both groups reported high satisfaction, scores were significantly higher for women who chose RRSO than for those who continued with periodic ovarian cancer screenings \( (P < .001) \). Women were less satisfied overall when they felt the decision about whether to proceed with RRSO was a difficult one to make \( (P = .001) \). Tiller et al reported that, overall, after RRSO, 86.4% of women reported feeling decreased anxiety about ovarian cancer and a high degree of satisfaction with their decision to undergo the procedure.

For patients who elect RRSO before menopause, the inevitable next question is whether to initiate HT. The decision to use HT after RRSO in patients at high risk for ovarian cancer, especially those who are BRCA1- or BRCA2-positive, can be controversial given the potential to increase these patients’ already elevated risk of breast cancer. In a systematic review by Gordhandas et al evaluating the use of HT in BRCA1 and BRCA2 patients who undergo RRSO, there were clear benefits of HT on quality of life and sexual health, but data on bone health, cardiovascular health, and cognition were limited in this population. This systematic review identified four studies assessing breast cancer risk in BRCA patients (although only one study included both BRCA1 and BRCA2, as the others were limited to BRCA1 patients), and none of them found an increased risk of breast cancer with the use of HT following RRSO. Ultimately, for high-risk patients who undergo RRSO before age 45 and who do not have a personal history of hormone-sensitive breast cancer precluding
them from using HT, the decision to use HT should be individualized and account for the impact of early menopause on long-term health and wellness in addition to any increased risk for breast cancer.36

A few studies have examined the safety of assisted reproductive technologies in women at high risk for ovarian cancer, particularly women who carry BRCA1 and BRCA2 mutations. Gronwald et al evaluated 941 case–control pairs of women from 72 medical centers across 20 countries with and without BRCA1 or BRCA2 mutations to assess whether undergoing fertility treatment was associated with an increased risk of ovarian cancer.37 They found no significant relationship between any fertility medications or in vitro fertilization treatment and the risk of subsequent ovarian cancer (OR 0.66, 95% CI 0.18–2.33).37 Similarly, Perri et al assessed 1,073 BRCA carriers, 164 of whom underwent some form of assisted reproductive technology, and found that fertility treatments were not associated with increased risk of epithelial ovarian cancer regardless of treatment type (overall age-adjusted OR 0.63, 95% CI 0.38–1.05; specific to clomiphene citrate, OR 0.87, 95% CI 0.46–1.63; gonadotropin, OR 0.59, 95% CI 0.26–1.31; in vitro fertilization, OR 1.08, 95% CI 0.57–2.06).38 No major professional societies provide recommendations on this topic. Usual practice is to provide assisted reproductive technology to patients who are at high risk for ovarian cancer following shared decision-making.

Guidelines from ACOG relating to patients with BRCA1 or BRCA2 mutations state:

[W]omen with BRCA mutations or who carry another actionable deleterious mutation predisposing to ovarian cancer should be offered risk-reducing BSO. ... The timing of risk-reducing BSO can be individualized based on the particular genetic mutation, the patient’s desires for future childbearing, and family history. Typically, risk-reducing salpingo-oophorectomy is recommended at age 35–40 years for BRCA1 carriers with the highest lifetime risk of ovarian cancer, whereas women with BRCA2 may consider delaying until age 40–45 years because of later onset of ovarian cancer.39(116)
NCCN guidelines also recommend RRSO between ages 35 and 40 years for BRCA1 mutation carriers and allowing for delay of RRSO until age 40–45 in BRCA2 carriers. Additionally, NCCN recommends consideration of RRSO for all BRIPI and RAD51C/D mutation carriers at age 45–50 years.32

The Society of Gynecologic Oncology guidelines additionally state, “In the event that [women with BRCA1 or BRCA2 germline mutations] opt to delay or forego risk-reducing BSO, they should be counseled regarding risk-reducing salpingectomy when childbearing is complete followed by oophorectomy in the future, although safety of this approach has not been studied.”40(p1) The Society of Gynecologic Oncology further states, “Women with BRCA1 or BRCA2 mutations should consider taking oral contraceptive pills to reduce their ovarian cancer risk.”41(p2112)

Regarding the use of routine ovarian cancer screening with serum CA 125 assessment or transvaginal ultrasonography, ACOG states this approach “generally is not recommended” and continues, “Transvaginal ultrasonography or measurement of serum CA 125 level may be reasonable for short-term surveillance in women at high risk of ovarian cancer starting at age 30–35 years until the time they choose to pursue risk-reducing BSO, which is the only proven intervention to reduce ovarian cancer-specific mortality.”39(pe115)

**RESEARCH GAPS AND OPPORTUNITIES**

- Development of best practices to mitigate ovarian cancer treatment-related changes in sexuality, as well as improved approaches to the management of long term treatment effects such as neuropathy, depression, and pelvic floor dysfunction.
- Understanding of stigma following hysterectomy for ovarian cancer and development of best practices to enhance body-positive treatment.

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- Optimization of ovarian cancer screening for high-risk persons who choose to delay or forego RRSO.
- Understanding of how to safely use available assistive reproductive technologies, such as cryopreservation and ectopic transplantation, in patients with ovarian cancers.
- Development of best practices for communication between patients and clinicians to optimize patient comfort and understanding.

REFERENCES


The authors provided this information as a supplement to their article.


