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Executive Summary

Executive Summary of the Uterine Cancer Evidence Review Conference

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The Centers for Disease Control and Prevention recognized the need for educational materials for clinicians on the prevention and early diagnosis of gynecologic cancers. The American College of Obstetricians and Gynecologists convened a panel of experts in evidence review from the Society for Academic Specialists in General Obstetrics and Gynecology and content experts from the Society of Gynecologic Oncology to review relevant literature, best practices, and existing practice guidelines as a first step toward developing evidence-based educational materials for women's health care clinicians about uterine cancer. Panel members conducted structured literature reviews, which were then reviewed by other panel members and discussed at a virtual meeting of stakeholder professional and patient advocacy organizations in January 2021. This article is the evidence summary of the relevant literature and existing recommendations to guide clinicians in the prevention, early diagnosis, and special considerations of uterine cancer. Substantive knowledge gaps are noted and summarized to provide guidance for future research.

(Obstet Gynecol 2022;139:626–43)
DOI: 10.1097/AOG.0000000000004711

The Centers for Disease Control and Prevention previously launched a campaign in collaboration with the American College of Obstetricians and Gynecologists (ACOG) to increase patient and clinician awareness of early-onset breast cancer.[1] The Centers for Disease Control and Prevention expanded the project

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Supported by the Centers for Disease Control and Prevention (CDC) of the U.S. Department of Health and Human Services (HHS) under cooperative agreement number 6 NU38OT000287-03-03, which was awarded to the American College of Obstetricians and Gynecologists (ACOG).

The authors thank Jean Riedlinger, MSLS, AHIP, Yvonnada McNeil, MSLS, Elizabeth York, MPH, and Jessica Butler, MPH, for their assistance with the database searches; Dana Trevas, Nancy O'Reilly, MHS, PMP, and Apurvi Shah, MPH, for facilitating the management of the review and editing process; and the individuals who attended the January 2021 Uterine Cancer Evidence Review Conference, listed in Appendix 1 online at http://links.lww.com/AOG/C620, for their discussion, input, and comments.

Participation in this project as an attendee of the Evidence Review Conference does not constitute organizational or individual endorsement of the conclusions. Information in this article should not be construed as the official position or policy of, or should any endorsements be inferred by CDC, HHS, or the U.S. Government.

Each author has confirmed compliance with the journal's requirements for authorship.

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Financial Disclosure

David Chelmow is the president of ASCCP and immediate past president of the Council of University Chairs of Obstetrics and Gynecology, receives a stipend as the editor-in-chief of the Medscape Obstetrics and Gynecology Clinical Reference Book, and was on the American Board of Obstetrics and Gynecology Board of Directors during the evidence review and manuscript writing period. David Chelmow is a member of the United States Preventive Services Task Force (USPSTF). This article does not necessarily represent the views and policies of the USPSTF. Rebecca Brooks is a member of an AstraZeneca speakers' bureau related to ovarian cancer, a past advisory board member and consultant for GSK and Merck & Co., Inc., and a past non-branded speaker for Clinical Care Options. Sangini Sheth is a past consultant for Merck & Co., Inc., and a research study grant recipient (drug only: HPV vaccine) from Merck & Co., Inc. She was paid costs of travel and meeting registration (paid directly) and received honoraria payment for an education course from the ASCCP. She also has research grants from the NIH and CDC for studies unrelated to the submitted work. Brett Worly is an unpaid speaker for AbbVie, Inc. All authors received a one-time payment from ACOG for their participation in the development of uterine cancer educational materials.

ISSN: 0029-7844/22

with ACOG to include educational material for clinicians for early diagnosis and prevention of gynecologic cancers. Uterine cancer is the most common gynecologic cancer. There were 65,620 new cases (3.6% of all new cancer cases) and 12,590 deaths (2.1% of all cancer deaths) projected for 2020. Rates rose on average 1.3% per year from 2007 to 2016.[2] Because of its effect on so many women, uterine cancer was chosen as the first gynecologic cancer for educational material development. To ensure these materials were based on the most current literature and guidelines, an extensive literature review was conducted. This article is the evidence summary, which is presented in detail in the Appendices 2–8, available online at http://links.lww.com/AOG/C620. The health care professional educational material is available online at acog.org.

METHODS

Methods for the evidence review and educational material development closely followed the process for the early-onset breast cancer project,[1] although virtual meetings replaced in-person meetings because of the coronavirus disease 2019 (COVID-19) pandemic. The American College of Obstetricians and Gynecologists convened an expert panel to identify the best evidence and practices from the literature and existing relevant guidelines. The panel was recruited from the Society for Academic Specialists in General Obstetrics and Gynecology to review and summarize the evidence. The panel was supplemented by representatives from the Society of Gynecologic Oncology (SGO). Panel members were selected based on expertise in evidence review and synthesis. The panel developed research questions and used the PICO criteria (P=patient, problem, or population; I=intervention; C=comparison, control, or comparator; O=outcome[s]) to frame the literature review.

Experts in literature searches from the ACOG Resource Center searched the Cochrane Library, MEDLINE (through Ovid), and PubMed (for references not indexed through MEDLINE) for articles published between January 2000 and October 2020. Literature was organized by level of evidence. Published guidelines were categorized separately from studies. A primary reviewer was assigned to each topic to review titles and abstracts, and then the entire manuscript when appropriate. Reference lists from relevant articles found in the search were also reviewed. Reviewers did additional searches as necessary, including extending the search range. Internet searches were performed using standard search engines to seek guidelines, recommendations, and tools that might not have been published in peer-reviewed publications. Relevant information was evaluated and compiled into an evidence summary template by a primary reviewer. Completed templates were then reviewed by a secondary reviewer. The primary and secondary reviewer worked together to revise the evidence summary in response to the secondary reviewer's comments.

The American College of Obstetricians and Gynecologists convened the Uterine Cancer Evidence Review Conference virtually on January 13, 2021, bringing together expert panel members and representatives from stakeholder professional and patient advocacy organizations (Appendix 1, http://links.lww.com/AOG/C620). The panel members who served as primary reviewers for each of the research topics prerecorded their presentations, which were viewed in advance by meeting participants, including the stakeholder representatives. At the meeting, expert panel members presented a brief summary of their evidence review findings, which was followed by an open comment and discussion period with conference attendees. Comments were integrated into the evidence review summary by the primary reviewer. The revised summaries were sent to the secondary reviewer for final review, and final revisions were made by the primary reviewer (see Appendices 2–8, http://links.lww.com/AOG/C620). The final evidence review summaries were used to develop the educational material (available online at acog.org).

In performing the review, there was significant overlap between the results of the literature searches for the research questions about risk factors and risk reduction. The appendices for these two topics present the full evidence summary for each (Appendices 3 and 4, http://links.lww.com/AOG/C620). For this executive summary, epidemiologic and retrospective studies from both searches are combined in the Risk Factors section, and the Risk Reduction section contains summaries of intervention trials and recommendations. Major society guidelines cited in the evidence reviews were replaced with the most current versions during the executive summary preparation.

When reporting results of individual studies, we used the terminology describing gender, race, and ethnicity from the source article. Studies almost uniformly used the term "women" or "females" to refer to the gender of those affected by uterine cancer. Although we acknowledge that uterine cancer can affect individuals of different genders who possess a uterus, we used the term "women" or "females" in this review to reflect the cited literature. In keeping with the most common categories of race and ethnicity used in national data collection, when we had a choice of terminology, we used "Black" to refer to non-Hispanic Black or African American individuals and "White" to refer to non-Hispanic White individuals. We used the term

"Hispanic," and not "Latinx," because "Latinx" was rarely used in any of the articles reviewed. Although some studies restricted their analysis to Hispanic White individuals, others included Hispanic individuals of any race. Given the lack of consistency in the literature, we used the term "Hispanic," without reference to race.

EPIDEMIOLOGY AND CLASSIFICATION

Uterine cancer is the fourth most common cancer in the United States, accounting for 7% of cancers affecting women.[2,3] Most cases are confined to the uterus at diagnosis, with local or regional disease in 21% of cases and distant disease in only 8%. The prognosis is typically good, with uterine cancer accounting for only 4% of female cancer-related deaths.[2] Uterine cancers can be divided into endometrial cancers affecting the epithelial lining and much less common mesenchymal malignancies, which represent only 3% of uterine cancers.[3]

Endometrial Cancer

Although endometrial cancer can affect women of all ages, it is most commonly diagnosed between ages 55 and 64 years, with a median age of 63 years.[4] Both the incidence and mortality rates have been increasing since 2007, with the mortality rate increasing faster.[2] Aggressive high-risk subtypes have become more frequent, which may explain why the mortality rate has increased more than the incidence rate. Endometrial cancer rates are also increasing significantly in Hispanic women younger than age 50 years.[5]

Traditionally, endometrial cancers have been classified into type 1 and type 2 cancers. Type 1 cancers are estrogen-driven, low-grade (grade 1–2) endometrioid tumors and account for approximately 65–80% of cases. These low-grade endometrial cancers are usually diagnosed at an early stage, with 80% limited to the uterus at diagnosis. The prognosis is usually good, with 5-year survival rates of 80–90% for patients with stage I disease. Type 2 cancers are more common in older women and are typically characterized by more aggressive behavior and worse prognoses. Extrauterine disease is more common at diagnosis, and the risk of recurrence of both local and distant disease is higher. Subtypes of type 2 cancers include serous carcinoma, clear cell carcinoma, carcinosarcoma, most grade 3 endometrioid carcinomas, and undifferentiated or dedifferentiated cancers. Although there are important nuances between these histologic subtypes, they are often grouped together because of their aggressive behavior and relatively poor prognoses compared with type I cancers.[3] (See Appendix 2 [http://links.lww.com/AOG/C620] for further details about the histologic subtypes.) Rates of type 1 cancer are highest in White women in Western populations; type 2 cancers disproportionately affect non-Hispanic Black women.[6]

Uterine serous carcinoma is the most common high-risk histology, accounting for 10% of endometrial cancer cases, but up to 40% of deaths.[7] These cancers demonstrate the loss of function of p53. Human epidermal growth factor receptor 2 overexpression is present in up to 62% of cases; it has been used as a therapeutic target, resulting in improved outcomes.[7]

Although the type 1 and 2 classification has been a useful framework for categorizing endometrial cancer, recent trends have shifted toward molecular-based risk stratification systems.[8,9] The Cancer Genome Atlas landmark trial performed an integrated analysis of the genome, transcriptome, and proteome of 373 endometrial carcinoma samples and identified four molecular subtypes that naturally clustered based on four distinct profiling patterns with associated survival differences (Table 1).[10] Molecular-based classification of endometrial cancer is likely the future of endometrial cancer care and is increasingly being used to inform treatment decisions.[11] Use of this classification approach may eventually replace decision making based on histology alone, and is being evaluated in an ongoing prospective trial.[12]

Uterine Sarcomas

Uterine leiomyosarcoma, endometrial stromal sarcoma, and undifferentiated uterine sarcoma are the three main types of uterine mesenchymal tumors (sarcomas). Leiomyosarcoma is the most common, with an incidence of 0.36 per 100,000 female life-years. Leiomyosarcomas make up 1% of all uterine cancers and 70% of uterine sarcomas. They are twice as common in Black women than White women.[13] Uterine leiomyosarcoma is an aggressive uterine malignancy. Patients with uterine leiomyosarcoma usually present at older than age 40 years, and the incidence increases significantly after age 50 years.[13–15] Leiomyosarcoma typically spreads hematogenously, and metastatic disease is frequently present at the time of initial resection.[13] The 5-year survival rate for stage I disease is only 55% and falls to 21.7% for stage IV disease.[16] Other rare stromal malignancies include adenosarcoma, rhabdomyosarcoma, and malignant perivascular epithelioid tumors. (See Appendix 2 [http://links.lww.com/AOG/C620] for complete evidence summary.)

RISK FACTORS

Age and Menopause

In the United States, endometrial cancer is significantly more common in women after age 50 years.[4]

Table 1. The Cancer Genome Atlas Endometrial Cancer Classification*

TCGA Class	% of Cases	Characteristics	Prognosis	Potential Treatment Implications
POLE ultramutated	7	POLE mutations often endometrioid, tumor-infiltrating lymphocytes present	Excellent, recurrences rare	Observation may be reasonable; ongoing clinical trials are using this classification for treatment selection.†
MSI hypermutated	28	High MSI, deficient MMR (*MLH1*, *PMS2*, *MSH2*, *MSH6* mutations); both epigenetic–somatic and germline (Lynch syndrome)	Intermediate	Radiation is beneficial; these patients are candidates for immunotherapy if cancer is recurrent.‡
Copy number low	39	*PTEN*, *PIK3CA*, *CTNNB1*, *ARID1A* mutations common, estrogen or progesterone receptor expression, wild type p53	Intermediate to good	These patients are highly likely to respond to hormonal therapy; PI3K/mTOR inhibitors are an option for metastatic disease.‡
Copy number high (serous-like)	26	High somatic copy number alterations, p53 usually abnormal or mutated	Poor	Chemotherapy, *HER-2*–targeted therapy if positive.§

TCGA, The Cancer Genome Atlas; POLE, DNA polymerase epsilon; MSI, microsatellite instability; MMR, mismatch repair; *HER-2*, human epidermal growth factor receptor 2.

* Data from Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497:67–73.

† van den Heerik A, Horeweg N, Nout RA, Lutgens L, van der Steen-Banasik EM, Westerveld GH, et al. PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer. Int J Gynecol Cancer 2020;30:2002–7.

‡ National Comprehensive Cancer Network. Uterine neoplasms. Version 1.2021 – October 20, 2020. Accessed December 7, 2020. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf

§ Fader AN, Boruta D, Olawaiye AB, Gehrig PA. Uterine papillary serous carcinoma: epidemiology, pathogenesis and management. Curr Opin Obstet Gynecol 2010;22:21–9.

One study showed that more than 75% of women diagnosed with endometrial cancer before age 25 years are obese (body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] 30 or higher).[17] Additional risk factors for endometrial cancer before age 50 years include not using combined hormonal contraceptives and first birth after age 30 years.[18,19] Uterine sarcomas occur most commonly during perimenopause and early menopause. Leiomyosarcomas have the highest incidence between ages 45 and 59 years. Endometrial stromal sarcoma incidence rates are steady starting at age 45 years.[20]

Lifestyle

Two large meta-analyses have shown progressively increasing endometrial cancer risk with increasing BMI. Women who are overweight (BMI 25–29) have a relative risk (RR) of about 1.3, and women who are obese (BMI 30 or higher) have an RR of about 2.5 compared with normal-weight women.[21,22] In a meta-analysis of 19 studies, a 5-unit increase in BMI was associated with a 1.59 (95% CI 1.50–1.68) increase in RR of endometrial cancer.[23] Obesity increases risk for uterine sarcoma as well (odds ratio [OR] 1.73, 95% CI 1.22–2.46).[24]

Physical activity is associated with a decreased risk of endometrial cancer.[25] Multiple prospective studies and meta-analyses have confirmed this protective role, regardless of BMI (most vs least physical activity: pooled RR 0.78, 95% CI 0.63–0.95).[26,27]

High glycemic index diets,[28–30] diets high in saturated fats,[31] and pro-inflammatory diets[32] are possibly associated with increased risk of endometrial cancer. Retrospective studies have shown increased endometrial cancer risk with high meat consumption and decreased risk with high fruit and vegetable intake.[25,33,34] A meta-analysis of 13 retrospective studies suggested an inverse association between isoflavone consumption and endometrial cancer (OR 0.81, 95% CI 0.74–0.89), but this was not shown in a randomized clinical trial.[35,36] Dietary fiber may be inversely associated with endometrial cancer. A meta-

analysis noted an RR of 0.82 (95% CI 0.75–0.90) for each 5 g/1,000 kcal of dietary fiber intake.[37] Antiinflammatory diets that include fish or other sources of omega-fatty acids,[38] coffee,[39] and healthy dietary patterns (high in vegetables, fruit, whole grains, olive oil, fish, poultry, and low-fat dairy)[40,41] have been associated with decreased endometrial cancer risk.

Smoking is associated with decreased endometrial cancer risk (RR 0.81, 95% CI 0.74–0.88), with larger decreases observed among smokers who are obese [42] and postmenopausal smokers taking hormone therapy (HT).[43] Alcohol appears to have no significant effect on endometrial cancer risk.[44]

Hormonal Risk Factors

Endogenous Hormones

Increased length of exposure to endogenous hormones has been associated with increased endometrial cancer risk. Early menarche[45] and later menopause[46] are both associated with increased risk. Late menarche is inversely associated with uterine sarcoma risk.[24] Pregnancy appears to be protective. Parous women have an RR of endometrial cancer of 0.69 (95% CI 0.65–0.74) compared with nulliparous women.[47] Risk decreases with increasing parity. Women with late first birth (age 35–39 years) had an RR of 9.14 (95% CI 3.33–25.05) for endometrial cancer.[48] Giving birth to one's last child after age 40 years decreased risk by 44% compared with giving birth to one's last child before age 25 years.[49]

Menopausal Hormone Therapy

A recent systematic review reported endometrial cancer risk was elevated in five out of six observational studies of unopposed estrogen therapy, with risk persisting more than 10 years after the end of treatment.[50] An older meta-analysis calculated a summary RR of 2.3 for estrogen therapy users compared with nonusers, with an RR of 9.5 in women with more than 10 years of use.[51] Estrogen-only replacement is not recommended in patients who still have their uterus, for whom combined HT with at least 7–10 days of progestin per month is typically recommended. In the WHI (Women's Health Initiative) study, patients taking combined HT had fewer endometrial cancers (hazard ratio [HR] 0.65, 95% CI 0.48–0.89) than women taking placebo.[52] Women with high BMIs using combined HT have reduced risk of endometrial cancer compared with nonusers. A meta-analysis found that women who are extremely obese (BMI 42) who had never used HT had an RR of endometrial cancer of 20.70 (95% CI 8.28–51.84) compared with combined HT users.[53] The WHI cohort study reported no statistically different levels of endometrial cancer in vaginal estrogen users compared with nonusers.[54] Testosterone therapy can cause atrophic or proliferative endometrium.[55]

Progestin Contraceptives

The Norwegian Women and Cancer Study demonstrated a profound reduction in endometrial cancer risk with the levonorgestrel intrauterine device ([IUD], ever use vs never use: RR 0.22, 95% CI 0.13–0.40), even after adjusting for BMI and other risk factors.[56] No studies evaluating progestin IUDs in women with obesity or a genetic predisposition to uterine cancer were identified. A Cochrane review showed reduced risk of endometrial polyps and endometrial hyperplasia among women using the levonorgestrel IUD who were taking tamoxifen, but the included studies were not powered to evaluate endometrial cancer risk.[57]

Combined Oral Contraceptives

Use of combined oral contraceptives was associated with a decreased risk of endometrial cancer in two meta-analyses, a population-based study, and a large prospective study in U.S. women.[58–61] In the most recent, the Danish Sex Hormone Register Study, current or recent combined oral contraceptive use significantly reduced endometrial cancer risk (RR 0.57, 95% CI 0.43–0.75). Risk reduction increased with longer duration of use and persisted for more than 10 years after discontinuation.[60] In the Black Women's Health Study, similar results were noted in a cohort of 47,555 women, with an incident rate ratio of 0.45 (95% CI 0.24–0.74) for women with more than 10 years of oral contraceptive use compared with never users.[62] Use of combined oral contraceptives was associated with decreased endometrial cancer risk in a cohort of women with Lynch syndrome (HR 0.39, 95% CI 0.23–0.64 for 1 year or more of contraceptive use vs less than 1 year).[63]

Tubal Ligation

Two large population-based cohort studies demonstrated a decreased risk of endometrial cancer among women who underwent tubal sterilization (standardized incidence ratio 0.66, 95% CI 0.5–1.0, and HR 0.73, 95% CI 0.65–0.83).[64,65] The mechanism of risk reduction is unclear.

Family History and Genetic Syndromes

Several genetic cancer syndromes increase the risk of uterine cancer. These syndromes are caused by pathogenic mutations or variants in tumor suppressor

genes, each with different lifetime risks (see Appendix 3 [http://links.lww.com/AOG/C620]).[66] The lifetime risk of endometrial cancer in patients with Lynch syndrome ranges from 13% to 57%.[66] Cowden syndrome (*PTEN* mutations) and Peutz-Jeghers syndrome (*STK11* mutations) increase endometrial cancer risk 5% to 10%. Hereditary retinoblastoma (*RB1* mutation) increases the risk of leiomyosarcoma. A number of studies examined the risk of serous-type uterine cancer among individuals with the *BRCA1* mutation, some of which showed a small association.[8,67–71] The National Comprehensive Cancer Network states that this association may reflect tamoxifen use rather than genetic predisposition.[68] A family history of endometrial cancer without known familial gene mutations is associated with an increased risk in first-degree relatives (RR 1.82, 95% CI 1.65–1.98).[72]

Medications

Though type 2 diabetes mellitus, obesity, and polycystic ovarian syndrome (PCOS) are associated with endometrial cancer, a 2018 meta-analysis did not show a decreased risk of endometrial cancer with metformin use (OR 1.05, 95% CI 0.82–1.35).[73] Aspirin use has been associated with a decreased risk of endometrial cancer among women with obesity (pooled RR 0.83, 95% CI 0.69–0.99) and of type I endometrial cancer (pooled RR 0.89, 95% CI 0.82–0.96).[74] Bisphosphonate use has been associated with a reduction in endometrial cancer risk (ever use vs never use: RR 0.73, 95% CI 0.58–0.93). Risk reduction is greatest in postmenopausal women and with longer duration of use.[75]

Prior Health History

Multiple meta-analyses have shown an increased risk of endometrial cancer with diabetes, with the most recent reporting an RR of 1.72 (95% CI 1.48–2.01).[76] Diabetes also increases risk of uterine sarcoma (OR 2.33, 95% CI 1.41–3.83).[24] A systematic review of 25 studies found hypertension to be an independent risk factor for endometrial cancer (RR 1.61, 95% CI, 1.41–1.85).[77] A meta-analysis of studies of metabolic syndrome found too much heterogeneity between studies and in metabolic syndrome diagnostic criteria to calculate a pooled RR but noted increased prevalence of metabolic syndrome among patients with endometrial cancer compared with a control group in the individual studies.[78] Infertility treatment does not appear to be associated with uterine cancer risk, although there appears to be increased incidence in some subgroups of women with infertility, including those with ovulatory dysfunction, progesterone deficiency, and obesity.[79] Polycystic ovarian syndrome is associated with a 2.89 OR (95% CI 1.52–5.48) of endometrial cancer.[80] Breast and ovarian cancer do not appear to increase uterine cancer risk, although related treatments such as tamoxifen and pelvic radiation do increase uterine cancer risk.

Some preexisting histopathologic abnormalities increase risk. A meta-analysis reported that 32.6% of women with complex endometrial hyperplasia had an occult endometrial cancer (95% CI 24.1–42.4%).[81] Using newer endometrial intraepithelial neoplasia criteria, patients with endometrial intraepithelial neoplasia had a pooled RR of 19.37 (95% CI 5.86–64.01) for progression to cancer.[82] A meta-analysis found a 1.12% and 4.93% risk of endometrial polyps containing malignancy in premenopausal and postmenopausal women, respectively.[83] (See Appendices 3 and 4 [http://links.lww.com/AOG/C620] for complete evidence summaries.)

RISK REDUCTION

Lifestyle Modifications

The large, prospective National Institutes of Health-AARP Diet and Health cohort study and the WHI Dietary Modification randomized controlled trial did not show a protective effect from dietary modifications.[84,85] We did not find any interventional trials specifically looking at risk reduction with physical activity. Given the many other health benefits of healthy diet and physical activity, patients should be counseled to follow national recommendations.[86,87]

Weight Reduction

We found no specific intervention trials of weight reduction for endometrial cancer risk reduction. One retrospective study of self-reported intentional weight loss showed risk reduction in a number of cancers, but not endometrial cancer.[88] Patients in the WHI observation study who lost weight had a significant reduction in endometrial cancer risk, with an HR of 0.71 (95% CI 0.54–0.95) overall and an HR of 0.44 (95% CI 0.25–0.78) in women who are obese.[89] Bariatric surgery was associated with a decreased risk of endometrial cancer in a meta-analysis of retrospective studies (pooled RR 0.43, 95% CI 0.26–0.72).[90] Prospective studies demonstrate decreased endometrial proliferation on biopsy and a reduction in circulating endometrial cancer biomarkers after bariatric surgery.[91,92] Patients with BMIs 30 or higher should receive behavioral counseling given the many other benefits of weight reduction.[93]

Progestins and Oral Contraceptives

We found no specific interventional trials or recommendations for progestins or combined oral contraceptives for endometrial cancer prevention. Based on

the weight of the epidemiologic evidence, patients using these methods for clinical indications are likely experiencing endometrial cancer risk reduction as an ancillary benefit.

Other Medications

We found no interventional trials or recommendations for use of aspirin, metformin, or bisphosphonates for risk reduction.

Special Populations

Lynch Syndrome

Based on expert opinion, hysterectomy should be considered for risk reduction for women with Lynch syndrome who have completed childbearing.[66,69,94,95] Hysterectomy significantly reduces endometrial cancer incidence but not mortality in women with Lynch syndrome.[66,96] The National Comprehensive Cancer Network recommends considering risk-reducing hysterectomy for Lynch syndrome patients, with timing, "individualized based on whether childbearing is complete, comorbidities, family history, and [Lynch syndrome] gene, as risks for endometrial cancer vary by pathogenic variant."[66] The American College of Obstetricians and Gynecologists recommends discussing hysterectomy by a patient's early to mid-40s.[94]

Individuals With the *BRCA* Mutation

The National Comprehensive Cancer Network states the practitioner may discuss the risks and benefits of concurrent hysterectomy at the time of risk-reducing bilateral salpingo-oophorectomy for individuals with the *BRCA1* mutation, but also notes that further clarification of the magnitude of risk of serous uterine cancer is needed.[68]

Other Genetic Syndromes

We found no studies evaluating risk-reducing hysterectomy among women with Cowden syndrome, *PTEN* hamartoma tumor syndrome, or Peutz-Jeghers syndrome (pathogenic *STK11* variants). For patients with Cowden syndrome or *PTEN* hamartoma tumor syndrome, the National Comprehensive Cancer Network recommends that clinicians, "discuss option of hysterectomy upon completion of childbearing and counsel regarding the degree of protection, extent of cancer risk, and reproductive desires."[68]

SCREENING

Asymptomatic Average-Risk Patients

Limitations to effective screening for endometrial cancer in asymptomatic individuals include the low prevalence of disease and the most common symptom, abnormal uterine bleeding (AUB), usually arising at an early disease stage when high cure rates are possible. Our review found no study or major society recommendation supporting endometrial cancer screening in asymptomatic women at usual risk.

Studies of ultrasonography in women with postmenopausal bleeding have demonstrated low positive predictive value, varying between 0 and 0.2.[97] Screening tests would be expected to demonstrate even poorer performance in asymptomatic women, given the even lower disease prevalence. The literature review did not find studies assessing the use of endometrial sampling, hysteroscopy, or saline-infusion ultrasonography in asymptomatic women at usual risk. Endometrial cytology has been used in some countries as a screening modality, but its use has not demonstrated improvement in surgical stage at diagnosis or survival.[98] No studies were found supporting cervical cytology for screening for endometrial cancer. Three retrospective studies of different detection methods found no survival difference between cancers diagnosed in asymptomatic individuals and those diagnosed after postmenopausal bleeding.[98–100] These studies also suggest there is no difference in stage at diagnosis, although there was some variation in this outcome. The American Cancer Society first concluded that there was no indication for screening women without identified risk factors in 2001 and continues to maintain this conclusion.[101,102]

High-Risk Populations

Several professional societies recommend screening patients with Lynch syndrome (Table 2). These recommendations are largely based on expert opinion, and ACOG, the National Comprehensive Cancer Network, and the American Cancer Society all state that their recommendations have not been validated.[66,94,101] Although other genetic conditions, such as Cowden syndrome, Peutz-Jeghers syndrome, and Li-Fraumeni syndrome, confer an elevated risk of uterine cancer, we found no guidelines or studies to support screening in these populations. We found no guidelines or studies supporting endometrial cancer screening in individuals with the *BRCA* mutation.

Patients Using Tamoxifen

Tamoxifen users are at increased risk of developing benign polyps and endometrial cancer, with risk increasing with duration of use.[103] Tamoxifen use is associated with endometrial thickening, and there are no established thresholds for ultrasonographic measurement of endometrial thickness in this population. Two studies found that transvaginal ultrasonography

Table 2. Recommendations for Endometrial Cancer Screening in People With Lynch Syndrome

Source	Screening Recommendations
American Cancer Society*	Offer annual screening with endometrial biopsy beginning at age 35 y.
NCCN†	Consider screening using endometrial biopsy every 1–2 y starting at age 30–35 y. Transvaginal ultrasonography can be considered at the clinician's discretion in postmenopausal women. Transvaginal ultrasonography is not recommended as a screening tool in premenopausal women.
ACOG and SGO‡	Offer endometrial biopsy every 1–2 y starting at age 30–35 y.

NCCN, National Comprehensive Cancer Network; ACOG, American College of Obstetricians and Gynecologists; SGO, Society of Gynecologic Oncology.

* Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. CA Cancer J Clin 2001: Jan-Feb; 51(3):38–75.

† National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: genetic/familial high-risk assessment: colorectal (version 1.2020). Accessed November 30, 2020. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

‡ Lynch syndrome. Practice Bulletin No. 147. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014;124:1042–54. doi:10.1097/01/AOG/0000456325.50739/72

of asymptomatic premenopausal and postmenopausal women taking tamoxifen yields a high false-positive rate, leading to unnecessary intervention.[104,105] The American College of Obstetricians and Gynecologists, the National Cancer Institute, and the American Cancer Society recommend against routine screening.[101,106,107] Because emerging evidence suggests tamoxifen users with baseline endometrial polyps are more likely to develop atypical hyperplasia, ACOG states there may be a role for pretreatment screening before initiation of tamoxifen therapy.[106] (See Appendix 5 [http://links.lww.com/AOG/C620] for complete evidence summary.)

EARLY DIAGNOSIS

Postmenopausal bleeding is the presenting symptom in 91% of women with endometrial cancer.[108,109] Ten percent of women have bleeding in the first year after menopause.[110] The pooled risk of endometrial cancer in women with postmenopausal bleeding is 9%.[108] In a U.K. study, 41 of 85 women with endometrial cancer reported that they were not aware that bleeding was a sign of possible cancer.[111]

Techniques for Evaluation

Transvaginal Ultrasonography

Transvaginal ultrasonography is commonly used for first-line evaluation in patients with postmenopausal bleeding. In a meta-analysis, the sensitivity and specificity for endometrial cancer detection with an endometrial thickness threshold of 5 mm were 90% and 54%, and with a threshold of 3 mm, they were 98% and 35%, respectively.[112] For premenopausal women with AUB, multiple studies have shown saline-infusion ultrasonography to be superior to transvaginal ultrasonography in the detection of intracavitary pathology.[113–115] One study compared endometrial thickness to surgical or sonohysterogram findings in premenopausal patients and found endometrial thickness to be inadequate for excluding abnormalities.[116] The American College of Obstetricians and Gynecologists states that ultrasonographic measurement of endometrial thickness in premenopausal women has no diagnostic value and should not be performed.[117]

Office Endometrial Sampling

Office-based endometrial sampling is minimally invasive and cost-effective. The Pipelle catheter is an accurate method of endometrial sampling, with detection rates for endometrial cancer of 99.6% in postmenopausal women and 91% in premenopausal women.[118] The pooled sensitivity of office endometrial sampling for the diagnosis of endometrial cancer was 100% in studies using dilation and curettage (D&C) and 90% in studies using hysteroscopy with biopsy or curettage as the reference standard. Specificity for both ranged from 99% to 100%.[119] The accuracy of office endometrial biopsy is more limited with an inadequate specimen or if the endometrial pathology is not global.[120] In a meta-analysis of 11 studies, the posttest probability of endometrial cancer with a negative biopsy was 0.9%.[121] The SGO and ACOG both recommend that persistent AUB should be further evaluated, with the SGO specifying use of hysteroscopic-guided biopsy.[8,120]

Diagnostic Hysteroscopy

A meta-analysis of studies of hysteroscopic visualization in premenopausal and postmenopausal women showed a positive hysteroscopy has a high likelihood ratio (LR) for presence of endometrial cancer, but a negative hysteroscopy has only a moderate LR for ruling out cancer. Diagnostic hysteroscopy is highly accurate for diagnosing endometrial cancer among premenopausal and postmenopausal women with

AUB when there is adequate visualization of the uterine cavity (LR for positive result 60.9, 95% CI 52.1–72.5). A negative hysteroscopy alone is less accurate for the exclusion of endometrial cancer (LR for negative result 0.15, 95% CI 0.13–0.18), and diagnosis of endometrial hyperplasia is also more limited (positive result LR 10.4, 95% CI 9.7–11.1; negative result LR 0.24, 95% CI, 0.22–0.25).[122] The meta-analysis did not look at hysteroscopic visualization in combination with endometrial sampling, as is typically practiced. In one study, office hysteroscopy had a positive predictive value of 96% and negative predictive value of 98% when compared with histology at the time of hysterectomy.[123] Office-based hysteroscopy with guided biopsies can also be used.[120]

Evaluation of Postmenopausal Bleeding

The American College of Obstetricians and Gynecologists and the SGO recommend initial evaluation with either transvaginal ultrasonography or endometrial sampling.[8,124] In the setting of insufficient tissue on endometrial sampling, transvaginal ultrasonography can be used. If endometrial sampling is negative and the bleeding persists or recurs, hysteroscopy with D&C is recommended. The American College of Obstetricians and Gynecologists recommends using an endometrial thickness of greater than 4 mm to prompt endometrial sampling if starting evaluation with transvaginal ultrasonography.[124] Endometrial sampling in patients with postmenopausal bleeding using the Pipelle catheter is as effective and less costly than D&C, even after accounting for sampling failure, further supporting initial office-based evaluation.[125] In a cost-effectiveness analysis from the United Kingdom, a strategy using transvaginal ultrasonography with a threshold of 5 mm was the least expensive. Transvaginal ultrasonography using a threshold of 4 mm for endometrial sampling was similar in cost-effectiveness to endometrial sampling for initial evaluation.[126]

Detecting Endometrial Cancer in Premenopausal Patients

The American College of Obstetricians and Gynecologists recommends endometrial sampling in patients with AUB who are older than 45 years as a first-line test. The American College of Obstetricians and Gynecologists also recommends sampling in patients younger than age 45 years with risk factors, including history of unopposed estrogen exposure (such as seen in obesity or PCOS), failed medical management, and persistent AUB.[120] The International Federation of Gynecology and Obstetrics states, "for those at increased risk, endometrial biopsy is probably warranted."[127] The National Institute for Health and Care Excellence recommends hysteroscopy for patients with heavy and abnormal bleeding, with consideration of biopsy at the time of hysteroscopy for patients at high risk for endometrial pathology.[128] The SGO recommends endometrial sampling if the patient has risk factors or the workup of the bleeding is negative.[8]

Evaluation of Incidental Findings in Asymptomatic Patients

Among asymptomatic postmenopausal women, an increased endometrial thickness of 4 mm or more on transvaginal ultrasonography has poor accuracy for the diagnosis of endometrial cancer.[97,129] In a decision analysis, an endometrial thickness of more than 11 mm in asymptomatic postmenopausal women conferred similar risk for endometrial cancer (6.7%) as a patient with postmenopausal bleeding and an endometrial thickness of more than 5 mm (7.3%).[130] In a meta-analysis, the prevalence of malignancy in endometrial polyps was 2.73% overall (1.12% for premenopausal women and 4.73% for postmenopausal women). Asymptomatic women had a lower risk of malignancy (1.89%) compared with symptomatic women (5.14%, $P<.001$).[83] The American College of Obstetricians and Gynecologists states that management of endometrial polyps can be expectant or surgical depending on patient symptoms and risk factors for malignancy. Abnormal uterine bleeding is an indication for polypectomy.[131] We found no guidelines regarding evaluation or treatment of asymptomatic postmenopausal women with incidental endometrial polyps.

Cervical Cytology Findings Prompting Uterine Cancer Evaluation

The 2014 Bethesda System recommends reporting benign-appearing endometrial cells for women aged 45 years and older, and endometrial assessment is recommended for postmenopausal women.[132,133] In a systematic review of 22 studies, the prevalence of normal endometrial cells on cervical cytology was 0.7% (95% CI 0.4–1.4%) in women aged 40 years and older. Seven percent (95% CI 4–10%) of patients with normal endometrial cells on cytology had endometrial hyperplasia or cancer.[134] The 2019 ASCCP Risk-Based Management Consensus Guidelines recommend endometrial sampling for postmenopausal women with endometrial cells on cytology. They do not recommend evaluating asymptomatic premenopausal women with benign appearing endometrial cells. They recommend endometrial sampling in

conjunction with colposcopy and endocervical sampling in nonpregnant patients 35 years or older with all categories of atypical glandular cells or adenocarcinoma in situ on cytology. They also recommend endometrial sampling for nonpregnant patients younger than age 35 years with these findings and risk factors for endometrial neoplasia. For patients with atypical endometrial cells, preferred management is endometrial and endocervical sampling alone, but colposcopy is acceptable as part of the initial evaluation.[133] (See Appendix 6 [http://links.lww.com/AOG/C620] for complete evidence summary.)

HEALTH DISPARITIES

Significant uterine cancer health disparities were noted in the evidence review, including higher mortality and poorer survival for Black women than for any other racial or ethnic group. Black women were also much less likely than White women to receive evidence-based care. These differences were important enough that panel members and stakeholder representatives agreed that the topic merits its own summary. Please see the companion health disparities summary, "Health Disparities in Uterine Cancer: Report From the Uterine Cancer Evidence Review Conference."[135] Our review found no articles meeting inclusion criteria on uterine cancer risk among individuals who do not identify as cisgender or females.

DIAGNOSIS AND CARE COORDINATION

History

Medical history is important to detect endometrial cancer, as well as to assess patients with a new diagnosis. Relevant risk factors include age, obesity, use of unopposed estrogen, medical comorbidities (including PCOS and type 2 diabetes mellitus), atypical glandular cells on cervical cytology, and family history of gynecologic malignancy.[117,124] Postmenopausal bleeding is the most common symptom of endometrial cancer and warrants evaluation.[117,136,137] Our review did not identify studies establishing an age after which continued menstrual bleeding is abnormal. A systematic review did not find any studies about counseling or education interventions, but counseling postmenopausal women about the significance of bleeding may be important given this unmet need.[138]

Family History and Genetics

Endometrial cancer may be the presenting cancer in approximately 50% of patients with Lynch syndrome.[139,140] Any patient with a known family history of Lynch syndrome should be referred to a genetic counselor or tested for Lynch syndrome. Patients with a personal history of colorectal cancer or endometrial cancer who are diagnosed younger than age 50 years, who have another Lynch-related cancer, who have any relative with a Lynch-related cancer younger than age 50 years, or who have two or more relatives with a Lynch-related cancer at any age should also be evaluated for Lynch syndrome. The National Comprehensive Cancer Network recommends universal testing of endometrial carcinomas for mismatch repair proteins or microsatellite instability. Patients with abnormalities on genetic testing of their tumor and those with a significant family history of endometrial or colorectal cancer should be referred for genetic counseling and testing. Genetic testing results can also help inform choice of treatment options.[3]

Evaluation

The pelvic examination is important to evaluate and confirm the source of bleeding; assess the size, contour, and mobility of the uterus for surgical planning; assess for disease spread; and evaluate for other synchronous problems. Appropriate tissue sampling or transvaginal ultrasonography should be performed based on history and examination findings.[117] Ultrasonography is often performed in the initial evaluation of abnormal bleeding and can be useful for surgical planning when uterine size cannot be appreciated on examination because of body habitus or other factors. Magnetic resonance imaging is used for determining the primary cancer site (uterus vs cervix) and for assessing for cervical involvement or parametrial extension.[3] Because high-risk histologies, including uterine serous carcinoma, clear cell carcinoma, carcinosarcoma, and high-grade or undifferentiated carcinomas, often have extrauterine disease at time of diagnosis, computed tomography of the chest, abdomen, and pelvis and CA 125 evaluation may be considered as part of the initial evaluation.[3,141] For low-grade disease without other risk factors, chest X-ray is often sufficient. Chest X-ray evaluates for the presence of distant disease. Lung metastasis is rare in this setting but, if present, would significantly change the treatment plan. Additional information about the role of ovarian conservation and treatment alternatives in elderly or frail patients can be found in Appendix 7 (http://links.lww.com/AOG/C620).

Indications for Referral

Approximately 20% of patients with presumed early-stage disease are found to have metastatic disease at the time of surgery. The American College of Obstetricians

and Gynecologists recommends, "Physicians with advanced training and expertise in the treatment of women with endometrial cancer, such as gynecologic oncologists, understand the nuances of uterine cancer management, including the selection and sequencing of treatment modalities likely to benefit the individual patient. Patient outcomes are improved when high-volume surgeons in high-volume institutions render care, and this outcomes model typically is reproduced by standard gynecologic oncology practice."[117]

The World Health Organization endometrial precancer nomenclature has two categories: benign endometrial hyperplasia (nonneoplastic) and endometrial intraepithelial neoplasia (atypical hyperplasia, premalignant disease).[142] Endometrial intraepithelial neoplasia is the precursor to type 1 endometrial carcinoma. Approximately 42.6–62.5% of patients with a presumed diagnosis of endometrial intraepithelial neoplasia will have concurrent carcinoma, with an 11% risk of deep myometrial invasion.[143,144] The risk of having lymph node involvement with atypical hyperplasia was 3.3% in one study, and lymph node assessment influenced clinical decision making in approximately 28% of patients in another study.[145,146] This review did not identify recommendations regarding which patients with endometrial intraepithelial neoplasia should be referred to a gynecologic oncologist, the role of imaging in the evaluation of endometrial intraepithelial neoplasia, or the need for hysteroscopy or D&C before hysterectomy. If invasive cancer is found at the time of surgery, referral to a gynecologic oncologist and a second surgery may be indicated, with additional morbidity and risk. Additional information regarding the management of endometrial cancer, including the role of and approaches to lymph node assessment, can be found in Appendix 7 (http://links.lww.com/AOG/C620).

Uterine Sarcoma

Endometrial biopsy or curettage may detect uterine leiomyosarcoma in a subset of patients, but a negative test does not exclude malignancy, and there is no preoperative diagnostic test to reliably diagnose uterine sarcoma. Magnetic resonance imaging can be used to characterize uterine masses concerning for sarcoma.[13] Given the high risk of metastatic disease to distant sites, computed tomography of the chest, abdomen, and pelvis is recommended at the time of diagnosis.[3] Referral to a gynecologic oncologist should be considered if sarcoma is suspected based on an enlarging mass in a postmenopausal patient, evidence of metastases, or suspicious imaging findings. (See Appendix 7 [http://links.lww.com/AOG/C620] for complete evidence summary.)

SPECIAL CONSIDERATIONS

Survivorship is essential to the care of patients with uterine cancer. Women may have questions or concerns about future fertility or sexual health. Although chemotherapy, radiation, and surgery may prove lifesaving, their negative effects should be discussed with the patient and balanced against potential benefits in conjunction with patient priorities. These issues may need to be revisited throughout the evaluation and treatment course, as new relationships, understandings, information, and side effects may become relevant.

Fertility Preservation

An increasing number of women of reproductive age are being diagnosed with endometrial cancer and may want to preserve their fertility.[4] Consultation should be obtained from a gynecologic oncologist to ensure adequate risk assessment. Counseling should cover the risks and benefits of fertility preservation, treatments and side effects, chance of recurrence, relevant assisted reproductive techniques and their cost, and chances of pregnancy complications and successful live birth. Endometrial cancers in this age group are often early-stage, well-differentiated endometrioid type adenocarcinomas, with rare cases of myometrial invasion or lymph node metastasis.[147] The American Society for Reproductive Medicine recommends that patients of reproductive age undergoing potentially gonadotoxic therapies be informed by their health care professional about fertility preservation and future reproduction before treatment initiation. A collaborative, multidisciplinary, team-based approach may be helpful.[148]

Although fertility-sparing techniques limit complete surgical staging, the SGO and the National Comprehensive Cancer Network identify candidates for fertility-sparing treatment as those who strongly desire fertility, have a grade 1 tumor limited to the endometrium, have no contraindications for medical management, and are willing to accept the risks of nonstandard treatment.[3,9] Dilation and curettage is the optimal method to confirm grading and histologic differentiation of the endometrial cancer, in combination with contrast-enhanced magnetic resonance imaging to assess cervical, myometrial, adnexal, lymph node, or peritoneal involvement.[3,9,148]

Although hysterectomy is the definitive treatment, progestin treatment can be considered for patients with stage 1A, grade 1, minimally invasive endometrial cancer who desire fertility-sparing therapy. Continuous-dose oral therapy with medroxyprogesterone acetate or

megestrol acetate is frequently used.[9] Response rates to oral progestin therapy range from 48.2% to 76.2% of patients, with recurrence rates of 35.4–40.6% and a 28% live birth rate.[149,150] Several studies support the use of progestin-releasing IUDs.[151–154] Patients desiring fertility preservation should be placed on a continuous progestin-based therapy with megestrol, medroxyprogesterone, or the levonorgestrel IUD. Patients undergoing fertility-sparing progestin therapy should have endometrial sampling by office biopsy or D&C every 3–6 months, with a complete response expected by 6–12 months. None of the recommendations include serial imaging as part of surveillance. Treatment is typically continued for 6–12 months. Hysterectomy is recommended once childbearing has been completed.[3,9,154]

Sexual Health

Sexuality is complex and has many different components that may negatively or positively influence sexual health. Having a sexual partner, age, relationship issues, psychological and physical components, other aspects of overall physical health, endometrial cancer diagnosis, surgery that removes organs that may help define sexuality, chemotherapy, radiation, and a desire to please a sexual partner are some of the important contributors that affect the sexual health of patients with endometrial cancer.[155,156] In a cohort of patients with endometrial cancer, 40.5% were sexually active. Reasons for not being active include lack of a partner, lack of interest, physical problems, and fatigue.[157,158] Multiple studies have compared the effects of surgery on sexual dysfunction, and results vary, with no conclusive findings.[159–161] Studies of radiotherapy also found no consistent effect on sexual function for patients with endometrial cancer.[162–165]

We found very few studies on interventions to improve sexual health. A brief mindfulness-based cognitive behavioral therapy intervention showed improvement in a small group of survivors of cervical and endometrial cancer compared with a control group.[166] A study with no control group looked at vaginal dilator use in a cohort of women undergoing radiation for endometrial cancer. Although sexual activity increased over the course of therapy and for a year afterward, sexual enjoyment decreased, and vaginal dilator use did not prevent sexual problems or vaginal stenosis.[167] (See Appendix 8 [http://links.lww.com/AOG/C620] for complete evidence summary.)

RESEARCH GAPS AND OPPORTUNITIES

The evidence review and stakeholder discussion identified many research gaps and opportunities for uterine cancer, the highest priority of which are listed here. (See Appendices 2–8 [http://links.lww.com/AOG/C620] for a more thorough analysis of research gaps and opportunities for each topic.)

- Strategies to eliminate disparities in uterine cancer outcomes and to ensure equity in diagnosis and treatment of uterine cancer between racial and ethnic groups, regardless of socioeconomic and insurance type
- Obtaining data on risk factors, incidence rate, mortality rate, and survival of endometrial cancer among individuals who do not identify as cisgender females
- Strategies to mitigate rising mortality, including improving understanding of why high-risk histologic subtypes are increasing
- Better definition of patients at high risk for endometrial cancer, with evidence-based recommendations for surveillance and risk reduction
- Development of recommendations for the prevention of endometrial cancer in average-risk women, particularly diet and lifestyle modifications and progestin use
- Identification of risk factors and preventive measures and development of effective strategies for the early diagnosis of leiomyosarcomas and endometrial stromal sarcomas
- Comparative effectiveness studies of diagnostic algorithms for postmenopausal bleeding
- Optimal management of incidentally detected endometrial polyps
- Development of guidelines for referral of patients with endometrial intraepithelial neoplasia
- Evidence-based interventions for sexual health in patients with and survivors of uterine cancer
- Improved strategies and educational materials for patients and practitioners about warning signs of endometrial cancer, including at what point in the menopausal spectrum and age continuum continued bleeding is concerning
- Development of data-driven guidelines regarding the endometrial evaluation of patients taking tamoxifen
- Development of noninvasive diagnostic tests for endometrial cancer

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PEER REVIEW HISTORY

Received September 20, 2021. Accepted November 18, 2021. Peer reviews and author correspondence are available at http://links.lww.com/AOG/C621.